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1. terpenes
2. hydrocarbons
3. alcohols
4. aldehydes
5. ketones
6. acyclic terpenes
7. monocyclic "
8. oxides.
9. cyclogeraniolones.

TLMS



THE TERPENES

VOLUME I

*The Simpler Acyclic and Monocyclic Terpenes
and their Derivatives*

BY

J. L. SIMONSEN

SECOND EDITION REVISED

BY

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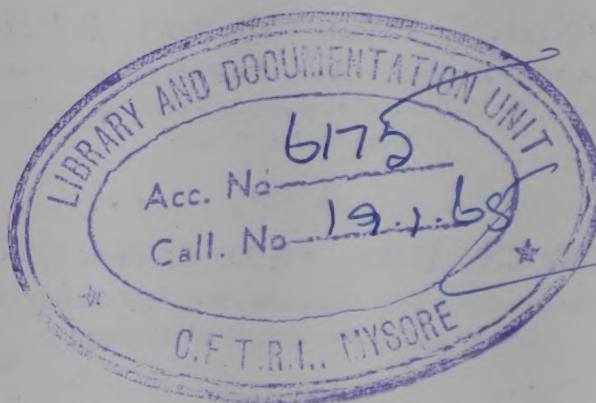
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Terpenes: Simple..

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PREFACE

Although the constituents of the various essential oils have been adequately dealt with in the English language by Parry, *The Chemistry of Essential Oils*, and by Finnemore, *Essential Oils*, with the exception of Brooks' monograph, *The Non-Benzenoid Hydrocarbons*, which covers a somewhat wider field, no book is available which deals with the chemistry of the terpenes. An attempt has been made in this volume to supply this deficiency, a description being given of the more important properties of the simpler acyclic and monocyclic terpenes and their derivatives. In order to keep the size of the book within reasonable limits it has been found necessary to include only those terpenes, containing ten carbon atoms, which occur in nature, although exception has been made in a few cases (sylvestrene, carvenone, terpin hydrate, etc.). Special attention has been directed to the methods used in the determination of constitution and synthesis, and it is hoped that the information which has been collected may stimulate research by British chemists in this important branch of organic chemistry, which owes so much to the pioneering investigations of Sir William Tilden and the synthetic researches of W. H. Perkin, jun.

It is proposed in a succeeding volume to discuss the dicyclic terpenes and sesquiterpenes.

The writer is indebted to Dr T. A. Henry for reading much of the book in manuscript and for many valuable suggestions; he desires also to acknowledge the valuable assistance rendered by Professor C. S. Gibson, O.B.E., and Dr R. S. Cahn in the reading of the proofs. He has further to thank Professor J. Read and the Council of the Chemical Society for their permission to reproduce the table on page 213.

J. L. S.

BANGOR

January 1931

PREFACE TO SECOND EDITION

The enhanced interest displayed in recent years in the chemistry of natural products has made it desirable to issue a revised edition of "The Terpenes." No attempt has been made to alter either the plan or the scope of the book. The literature, so far as the difficulties arising out of the war have permitted, has been consulted up to the end of 1945 and it has proved possible to include also some work of later date.

We are greatly indebted to Lt. Col. H. J. Holman, B.Sc., A.R.I.C. for undertaking the laborious task of checking all the literature references and also for the preparation of the author and subject indexes.

J. L. S.
L. N. O.

LONDON
May 1946

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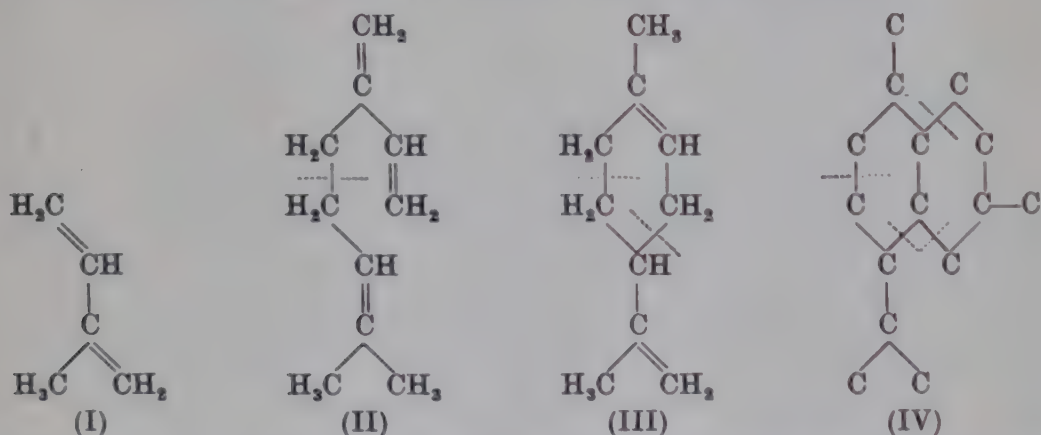
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INTRODUCTION

The essential oils of plants, which are present mainly in the flowers, fruits and leaves and also occasionally in the wood (camphor wood, sandalwood), consist of a complex mixture of ingredients comprising acyclic, alicyclic and aromatic substances. They are separated as a rule by distillation in steam, in which they are volatile, or by extraction with volatile or fixed solvents (enfleurage). In no case is the product so obtained homogeneous, but occasionally one ingredient may predominate, as is the case with oil of cloves, which consists almost entirely of eugenol.

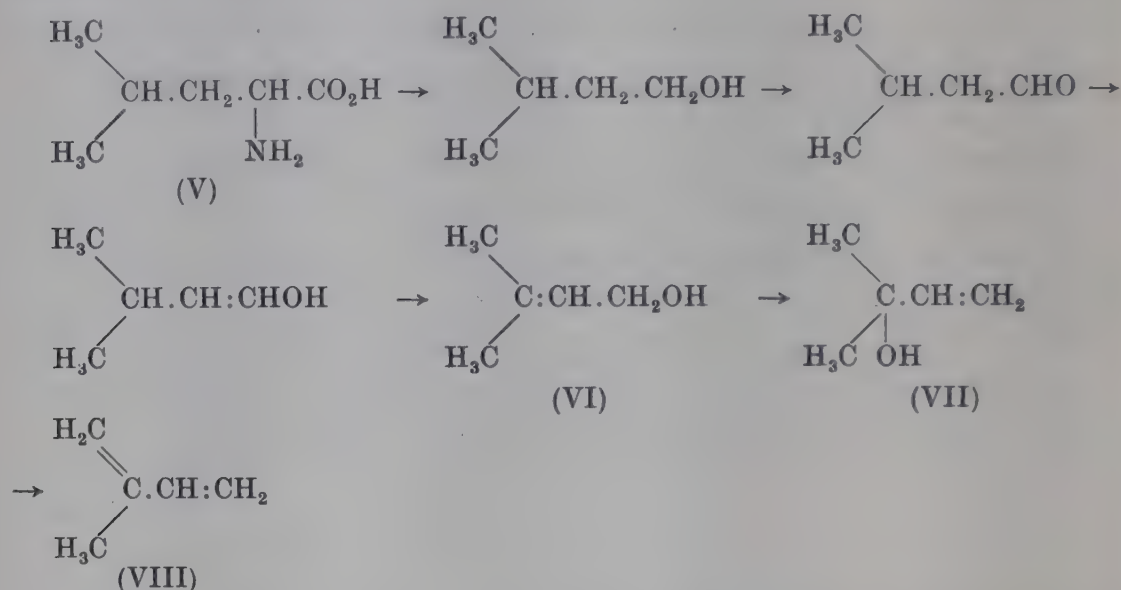
A consideration of the carbon skeleton of the acyclic and cyclic hydrocarbons and their derivatives, whether simple or complex, has revealed the interesting feature that they contain a repeated isopentane skeleton and that they may be regarded as derivatives of *isoprene*, C_5H_8 (I) (see below). Thus, for example, the simple hydrocarbons, *myrcene* (II) and *limonene* (III) may be constructed by the fusion of two isoprene nuclei, whilst sesquiterpenes (cadinene type (IV)) contain three such nuclei.



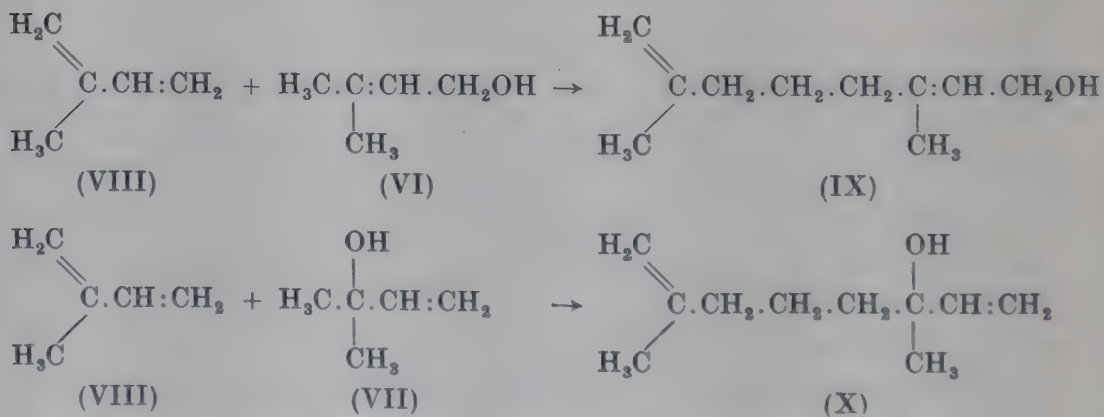
The so-called "isoprene rule" deduced from these observations has proved a most valuable working hypothesis for the elucidation of the structure, not only of the simpler terpenes, but also of the more complex sesquiterpenes and polyterpenes. It can, however, only be regarded as a working hypothesis, since several anomalous examples are known, including one which has been observed in the sesquiterpene series.* It does not, therefore, appear unlikely that other exceptions to the rule will be encountered.

* Gillam, Lynas-Gray, Penfold and Simonsen, *J.C.S.* 1941, p. 60.

The actual precursor of the terpenes is still obscure, and the part which they play in the plant metabolism unknown. Two views, which may ultimately prove to be complementary, have been advanced regarding their formation. Favorsky and Lébédéva* suggest that the parent substance of the terpenes is the amino-acid, *leucine* (V), formed by the degradation of proteins, which is converted into isoprene (VIII) by the reactions shown below:



The condensation of isoprene (VIII) with (VI) would then lead to *geraniol* (IX), or with (VII) to *linalool* (X). The facile polymerisation of isoprene to terpene hydrocarbons, alcohols and sesquiterpenes has been recorded by Wagner-Jauregg† and Lennartz.‡



* *Bull. Soc. chim.* 1939 [v], 6, 1350.

‡ *Ber.* 1943, 76, 831.

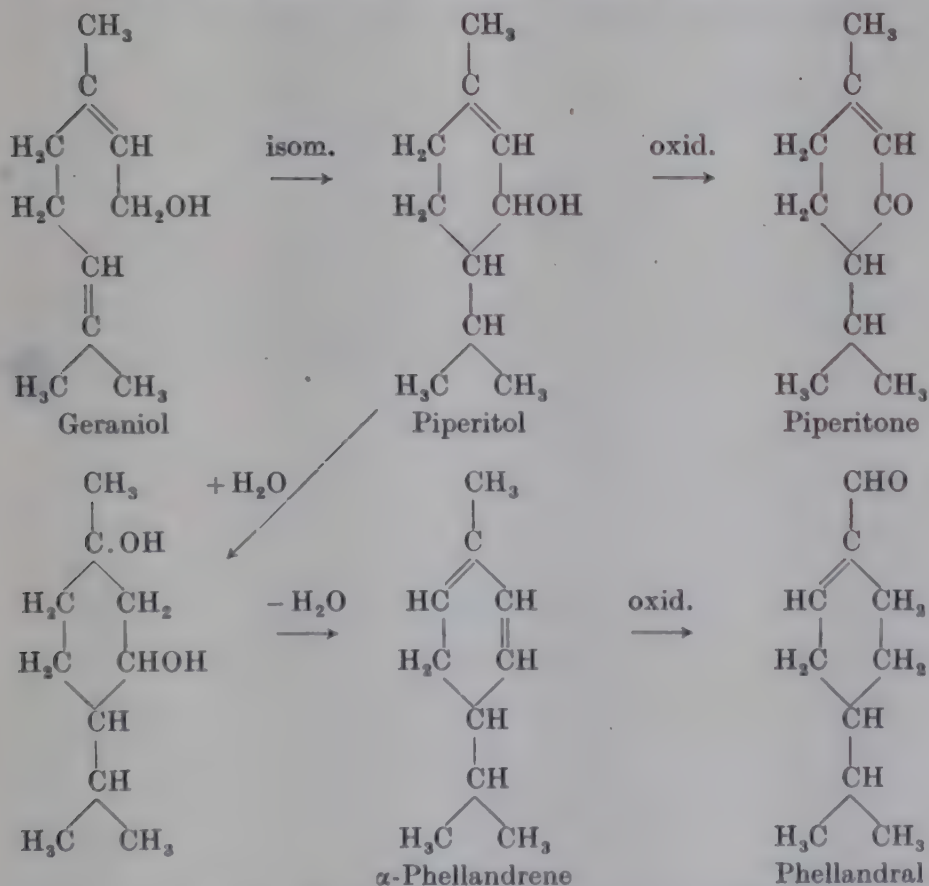
† *Annalen*, 1932, 496, 52.

The suggestion that *l*-leucine might be the precursor of the terpenes had been made previously by Leeman,* on the cytological evidence that the destruction of protoplasm precedes the formation of terpenes in certain plants. This simple mechanism for the formation of geraniol from leucine is of interest since, as pointed out by Read,† the alcohol possesses an unusual molecular structure; it contains a primary alcohol group activated by an $\alpha\beta$ -ethylenic linkage ($-\text{C}:\text{CH}.\text{CH}_2\text{OH}$) situated in close



proximity to a second active group $\left(\begin{array}{c} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{array} \right) > \text{C}:\text{CH}-$ also containing an ethylenic linkage. Owing to the great mobility of this grouping geraniol can be regarded as the parent substance of a great variety of cyclic terpenes and related bodies, the joint occurrence of which has been observed in plant products. The

(A) α -Phellandrene and related substances

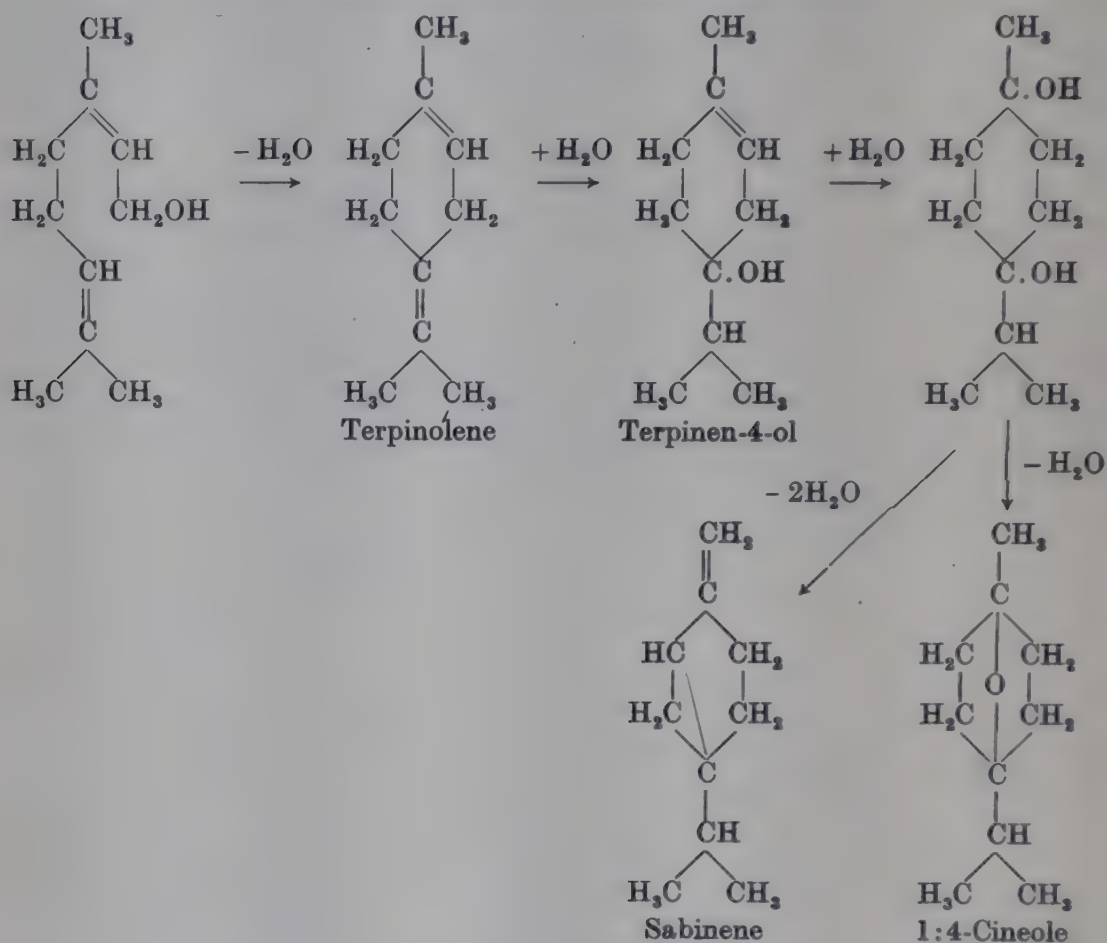


* *Nature*, 1929, 124, 946.

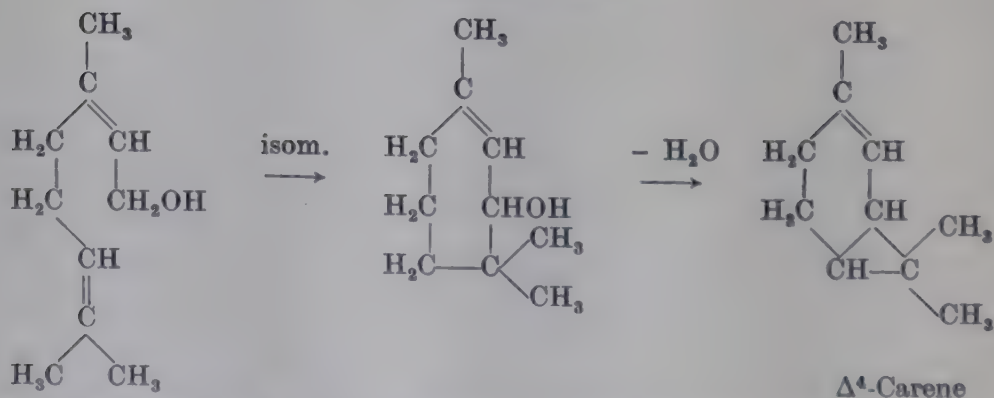
† *J.S.C.I.* 1929, 48, 786.

examples (A), (B) and (C), with some additions, are quoted from Read's memoir. (Substances to which no names are attached have not been found to occur in nature.)

(B) *Sabinene and related substances*



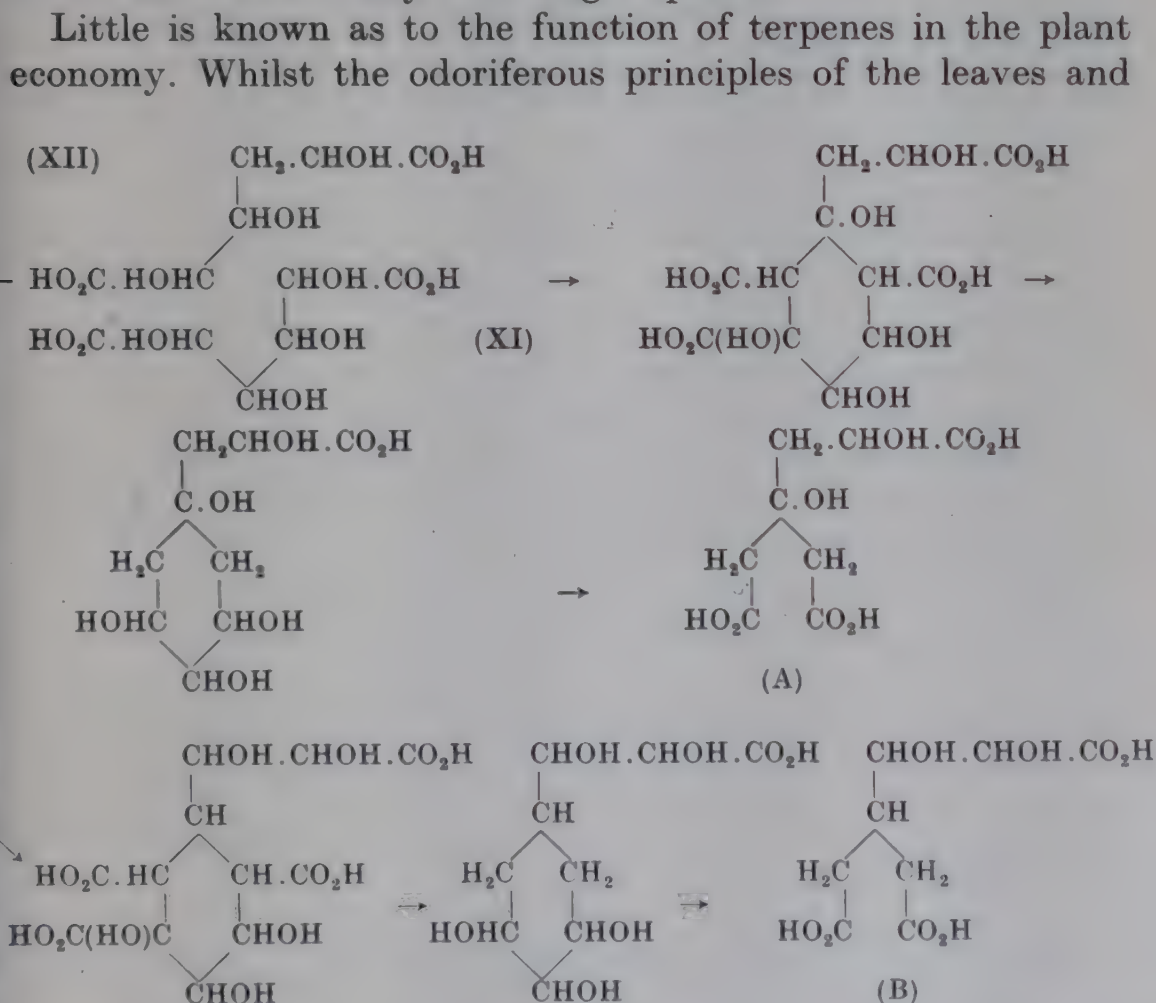
(C) Δ^4 -Carene*



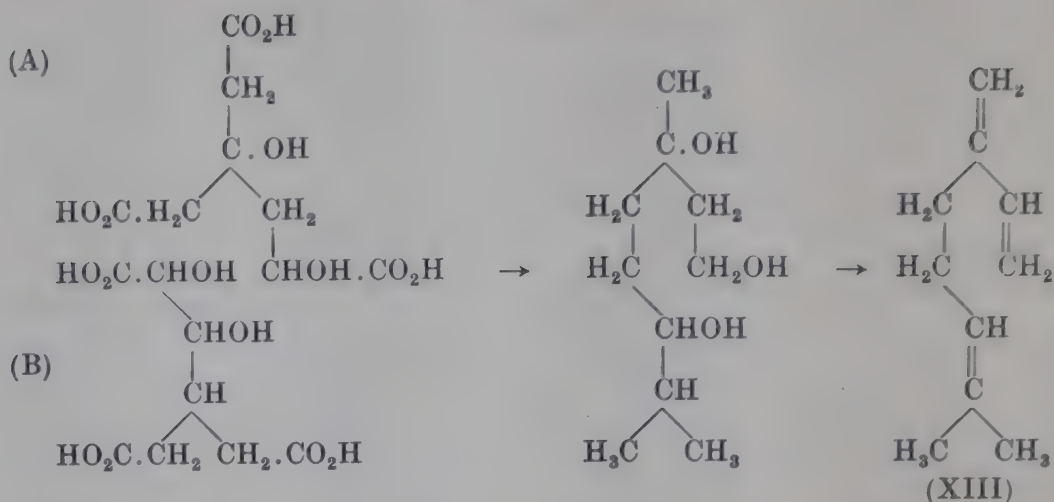
* An alternative and possibly simpler method involves the dehydration of piperitol (compare p. 287).

These examples, which could be extended to include also α -pinene, limonene, α -terpineol, etc., are sufficient to indicate that, starting from geraniol, it is possible by a single series of reactions to account theoretically not only for the formation, but also for the joint occurrence, of a number of terpenes and their derivatives.

It is not certain how far Leeman's observation can be generally applied and it is therefore not possible to reject a carbohydrate source. The most complete theory for a carbohydrate origin of the terpenes is due to Hall.* This may perhaps be most simply illustrated by his scheme for the formation of myrcene (XIII) from one molecule of *saccharic acid* (XI) and one of *meta-saccharonic acid* (XII). By variations of the process outlined below, the postulated intermediates (A) and (B) can give rise to all the known naturally occurring terpenes.



* *Chem. Reviews*, 1933, 13, 479; 1937, 20, 305; compare Singleton, *J.S.C.I.* 1931, 50, 989.



flowers can be assumed to be of use in the attraction of insects to the pollen, no such property can be ascribed to the oils present in other parts of the plant. In the latter case it is possible that they act as a protection against insect attack, but it would appear more satisfactory, in the absence of definite proof, to regard essential oils as waste products of the plant metabolism. Tyndall's theory that they have a "heat screening" effect is devoid of experimental justification.*

Attention may be directed here to one side of the study of essential oils which has aroused interest,[†] namely, the possibility of the use of these highly characteristic constituents as an aid to the differentiation of plant species. As the outcome of the important work of Smith on the constituents of the oils from the different species of *Eucalyptus*, Baker and Smith[‡] largely based their classification of the genus on the chemical characteristics of the oil derived from each species. The use of this method as an aid to the ordinary morphological classification has been advocated by Simonsen,[§] and would appear to be especially applicable in the case of grasses, such as the *Cymbopogons*, where the ordinary botanical methods have encountered great difficulties. Systematic work in this field with the refined methods now available should open up a wide and profitable field of research.

* Nicol, *Perfum. essent. Oil Rec.* 1936, **27**, 328.

† Barger, Presidential Address, Brit. Assoc., Section B, 1929; Hill, Presidential Address, Brit. Assoc., Section K, 1930; Parry, *Perfum. essent. Oil Rec.* 1941, **32**, 267; Penfold, *ibid.* 1942, **33**, 78.

‡ *A Research on the Eucalypts and their Essential Oils.*

§ Presidential Address, Indian Science Congress, 1928.

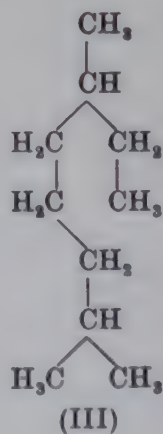
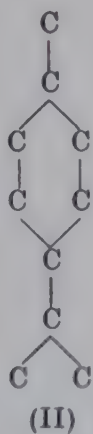
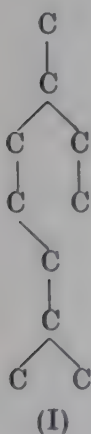
PART I

THE SIMPLER ACYCLIC TERPENES AND THEIR DERIVATIVES

INTRODUCTION

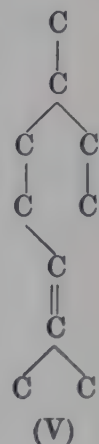
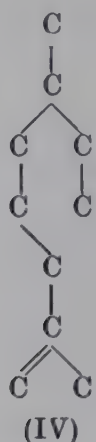
Although the acyclic terpenes and their derivatives, which occur in nature, are somewhat limited in number, they possess a wide scientific and technical interest. The fundamental investigations in this field were made during the decade 1890–1900 by Tiemann and Semmler in Germany and by Barbier, Bouveault and their collaborators in France. As a perhaps not unnatural outcome of the difficulty of this pioneering work, a controversy arose between these two schools. Subsequent research has shown that, although there may have been errors in detail, the work was in the main correct and the conflict in reality illusory. It lies beyond the scope of this monograph to discuss fully this controversy, and those interested should refer to the account given by one of the participators.*

As already mentioned, the simpler acyclic terpenes may be regarded as being formed by the union of two isoprene nuclei and may be represented by the skeleton formula (I), which, it will be observed, would pass by ring closure into the *p*-cymene structure (II). They can therefore be considered to be derivatives of the paraffinoid hydrocarbon 2:6-dimethyloctane (III).



* Semmler, *Die Ätherischen Öle*, vol. I.

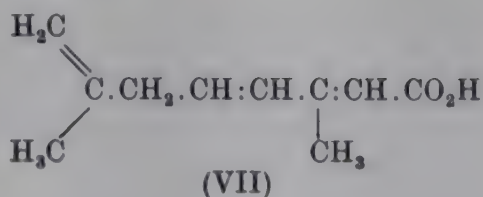
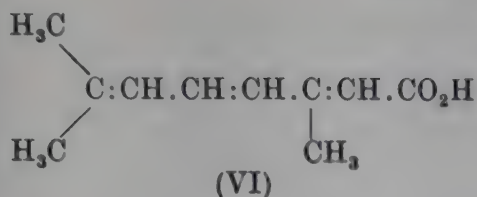
In such derivatives as contain one ethylenic linkage, this linkage is apparently, with one exception only, situated between the 1:2 or the 2:3 carbon atoms, so that they have the structures represented by the formulae (IV) and (V), designated by Semmler the dipentene (*isopropenyl*) and terpinene (*isopropylidene*) forms respectively.



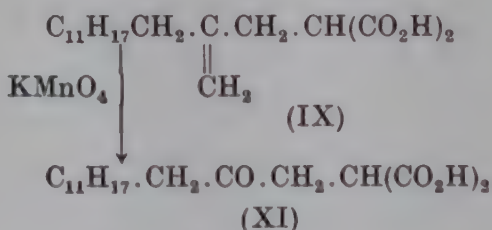
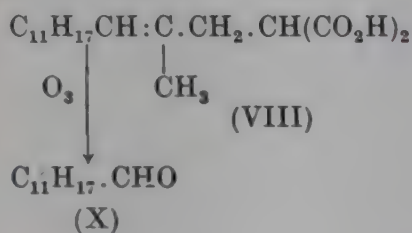
Much of the early controversy ranged round the position of this ethylenic linkage and in spite of numerous investigations the situation cannot yet be regarded as completely clarified. Since the majority of substances which have been examined are oils, adequate proof of homogeneity has been lacking, but the final conclusion reached, with which the authors concur, is that in nearly all cases these oils consist of a mixture of the *isopropenyl* and *isopropylidene* forms in varying proportions. The proportion in which each form is present has, as a general rule, been determined by oxidation, the yield of acetone and formaldehyde being estimated. In a few cases crystalline and apparently homogeneous solids have been examined and these would appear also to be inseparable mixtures. This has been shown to be the case with citronellal semicarbazone (p. 74), and two further interesting examples are dehydrogeranic acid and α -santalylmalonic acid.

Both natural and synthetic *dehydrogeranic acids* give on ozonolysis acetone and formaldehyde, the yield of acetone being approximately 60 per cent.* It is natural to deduce therefore that this acid is a mixture of (VI) and (VII).

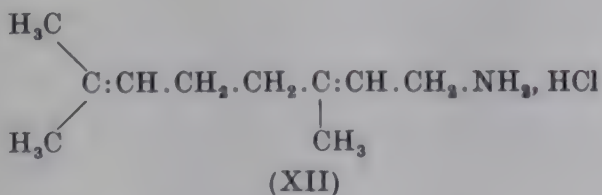
* Cahn, Penfold and Simonsen, *J.C.S.* 1931, p. 3134; Kuhn and Roth, *Ber.* 1932, 65, 1285.



On the basis of the absorption spectra of this acid and its homologues Kuhn and Roth maintain that the acid is represented by (VI), and they consider that the poor yield of acetone, with the simultaneous formation of formaldehyde, is due to the oxidation proceeding in an abnormal manner. We do not agree with this view since, if it be accepted, it would throw doubt upon all structures based upon oxidative degradation. Somewhat analogous is the observation made by Bradfield, Penfold and Simonsen* that *α-santalylmalonic acid* can be equally well represented by (VIII) or (IX), since on ozonolysis it yields solely *tricycloekasantal* (X) (or the related acid), whilst with potassium permanganate in alkaline solution the *keto-acid* (XI) is obtained.



It may of course be postulated that in neutral solution the acid exists as (VIII) whilst the sodium salt is derived from (IX), a suggestion involving facile tautomerism. It would be of considerable interest to examine the X-ray crystal structure of this acid, since it has been shown by Bateman and Jeffrey† that *geranylamine hydrochloride*, m.p. 145–146°,‡ is the pure *isopropylidene* derivative (XII).



* *J.C.S.* 1935, p. 311.

† *Nature*, 1943, 152, 446; Jeffrey, *Proc. Roy. Soc.* 1945, 183 A, 388.

‡ Sutton, *J.C.S.* 1944, p. 306.

It would therefore appear to us that at the present time the balance of the *chemical* evidence is in favour of the view that geraniol, citral and many other terpene derivatives are best regarded as "tautomeric" mixtures containing both the *iso*-propenyl and *isopropylidene* groups.

The value of molecular refraction and absorption spectra as hand-maidens in the determination of the structure of terpenes is too well established to require emphasis here. In recent years the use of the Raman spectra, both in the determination of structure and also of homogeneity, has become increasingly frequent. The use of this tool in terpene chemistry has been critically examined by Angus.* He concludes that at the present time the identification of the constituents of a mixture of terpenes by Raman spectra cannot give satisfactory results. This is partly due to the fact that there is little accurate data for the pure constituents. This is not surprising since, as mentioned above, the majority of terpenes are liquids, and evidence for their complete homogeneity is lacking; even small traces of impurities are liable to modify the lines of the main constituent. As is pointed out by Angus, the danger involved in the use of Raman spectra for the analyses of hydrocarbon mixtures is clearly shown in Snitter's work on camphenilene.† From the Raman spectra Snitter deduced that he had prepared nearly pure camphenilene containing only from 2–5 per cent. of apocyclene, and further that santene was completely absent. Subsequently, irrefutable chemical evidence was adduced‡ which showed that Snitter's camphenilene was essentially a mixture of apocyclene and santene. Although we have in the sequel given references to the more important papers recording Raman spectra, we do not consider that this physical method can at present be applied with advantage in the determination of structure or homogeneity.

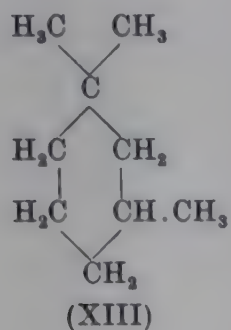
Of the general properties of the acyclic terpenes, reference need only be made to the ease with which they pass into cyclic derivatives. Cyclisation can proceed in two distinct ways, with formation (i) of derivatives of *p*-cymene, and (ii) of 1:1:3-

* *Ind. Acad. Sci.*, Raman Jubilee No., 1935, p. 529.

† *Bull. Inst. Pin.*, 1933, p. 209.

‡ Gratton and Simonsen, *J.C.S.* 1935, p. 1621; Komppa and Nyman, *Ber.* 1936, 69, 334; Lipp, *ibid.* p. 586.

trimethyl*cyclohexane* (XIII). The former, the monocyclic terpenes and their derivatives, are discussed in Part II, but the latter are more conveniently dealt with in this section (Chapter V).

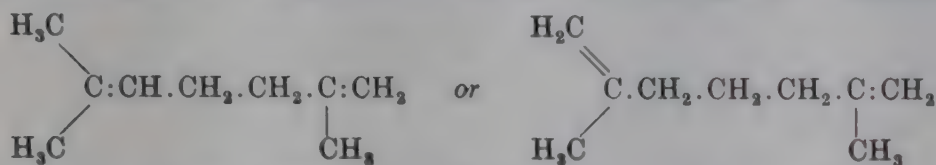


CHAPTER I

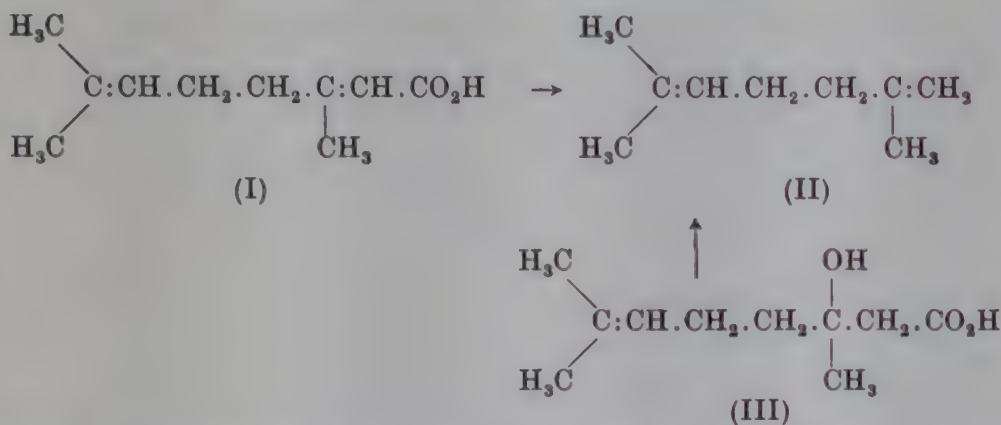
HYDROCARBONS

GERANIOLENE

(2:6-Dimethyl- Δ -^{2:6}-heptadiene or 2:6-Dimethyl- Δ ^{1:6}-heptadiene)

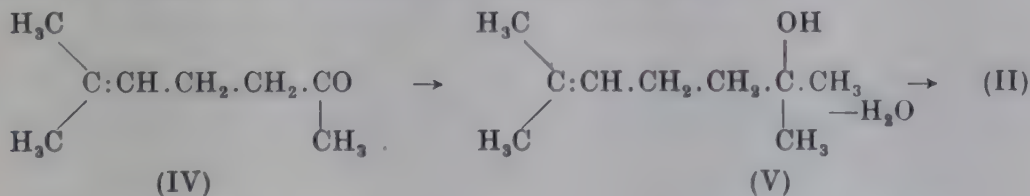


Geraniolene, C_9H_{16} (II), was first prepared by Tiemann and Semmler* by the distillation of *geranic acid* (I) at the ordinary pressure, when carbon dioxide was eliminated.



The hydrocarbon was described as an oil, b.p. 142–143°, d^{20}_D 0.757, n_D 1.4368, the presence of two ethylenic linkages being established by the preparation of a liquid *tetrabromide*.

Subsequently, Tiemann† prepared geraniolene by the distillation of *hydroxydihydrogeranic acid* (III), the synthesis of which is given on p. 87, whilst in the following year Grignard‡ obtained it by dehydration of the *alcohol* (V) formed by the action of methyl magnesium iodide on *methylheptenone* (IV).



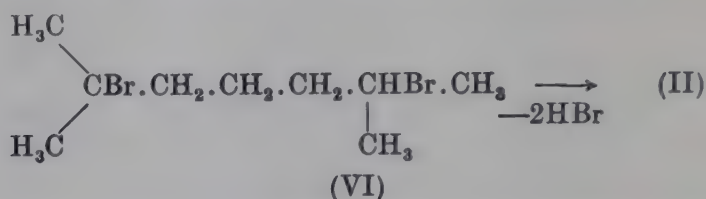
* Ber. 1893, 26, 2724.

‡ Thèse de Doctorat (1901), p. 81.

† Ibid. 1900, 33, 565.

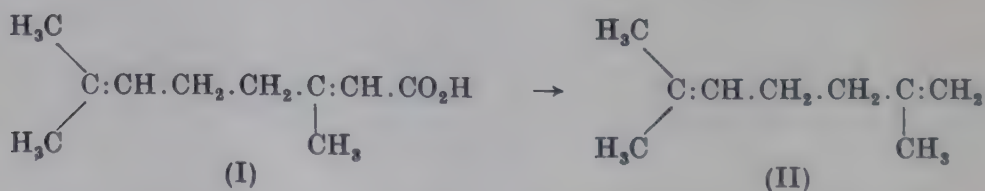
The constitution of geraniolene was considered to be established by its method of preparation, and also by the fact that on oxidation it gave amongst other substances acetone and levulinic acid, and formula (II) received general acceptance amongst other investigators in this field.*

Doubt as to the homogeneity of Tiemann and Semmler's hydrocarbon would appear to have been first expressed by Harries and Weil,[†] who prepared a hydrocarbon, which they considered to have structure (II), by the elimination of hydrogen bromide from 2:6-dibromo-2:6-dimethylheptane (VI).



The constitution of the hydrocarbon prepared in this manner, which had constants differing somewhat from those observed by Tiemann and Semmler (b.p. 140–142°, d^{22}_D 0.7626, n^{22}_D 1.4436), was determined by Harries and Türk,[‡] who showed that, on oxidation with ozone, levulinaldehyde was formed.

Auwers and Eisenlohr,[§] and Auwers and Moosbrügger,^{||} who have examined the physical constants of the geraniolene prepared by these different methods, conclude that in no case can the hydrocarbon be regarded as homogeneous. There can be little doubt that this view is correct. Geranic acid is always a mixture of the two acids represented by formulae (I) and (I a), and in all probability therefore geraniolene, as prepared by Semmler's method, is a mixture of the two hydrocarbons (II) and (II a).



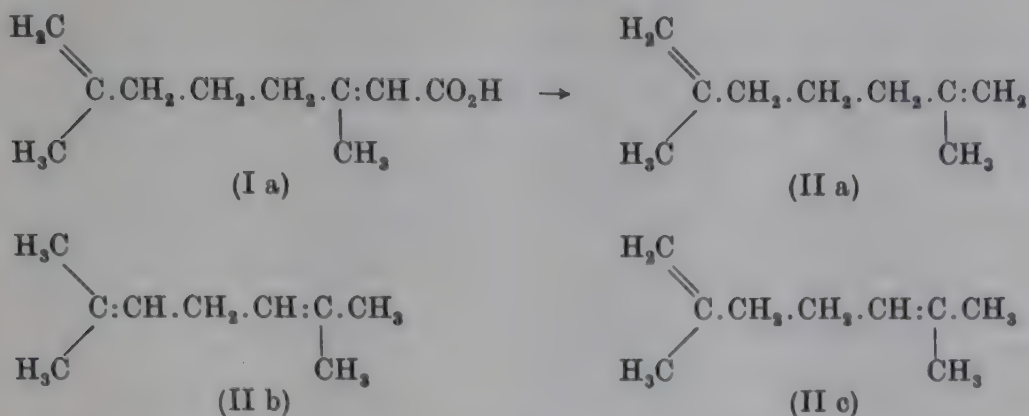
* Barbier, *Compt. rend.* 1899, **128**, 110; Sand and Singer, *Ber.* 1902, **35**, 3184; Rupe and Schlochoff, *ibid.* 1905, **38**, 1500.

[†] *Ber.* 1904, **37**, 846.

[‡] *Annalen*, 1905, **343**, 362.

[§] *J. pr. Chem.* 1910 [ii], **82**, 76.

^{||} *Annalen*, 1912, **387**, 183.

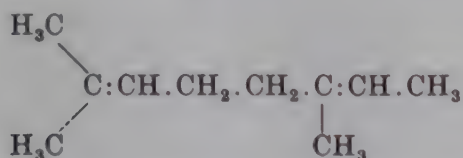


If the hydrocarbon is prepared by Grignard's method, it is possible that the hydrocarbons represented by formulae (II b) and (II c) may also be present.

When geraniolene is treated with sulphuric acid it undergoes cyclisation, yielding a mixture of hydrocarbons known as the *cyclogeraniolenes*, which are considered on p. 107.

DIHYDROMYRCENE

(2:6-Dimethyl- $\Delta^{2:6}$ -octadiene)



By the reduction of myrcene with sodium and alcohol, Semmler* prepared a hydrocarbon, $\text{C}_{10}\text{H}_{18}$, to which he gave the name dihydromyrcene. This hydrocarbon was regarded as 2:6-dimethyl- $\Delta^{2:6}$ -octadiene and was characterised by the preparation of a crystalline *tetrabromide*, m.p. 87–88°. A crystalline *tetrachloride*, m.p. 50°, has recently been prepared by Bloomfield.† In an earlier investigation, Semmler‡ had prepared by treatment of linalool with zinc dust at 225° a hydrocarbon, *linaloolene*, having the same composition, and this has since been shown to be identical with dihydromyrcene.§ According to Enklaar|| dihydromyrcene is also formed when either *ocimene* or *allo-ocimene* are reduced with sodium and alcohol, whilst Chablay¶ has described

* Ber. 1901, 34, 3126.

‡ Ber. 1894, 27, 2520.

|| Rec. trav. chim. 1907, 26, 157.

† J.C.S. 1944, p. 114.

§ Schimmel's Report, 1911, Oct. p. 128.

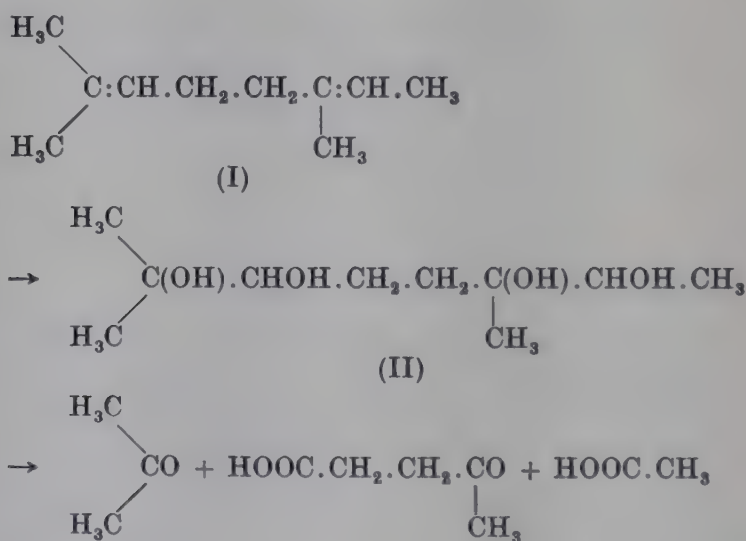
¶ Ann. chim. 1917 [ix], 8, 193.

its preparation from geraniol and linalool by treatment of these alcohols with sodamide in alcoholic solution. It does not, however, appear to be quite certain that all these hydrocarbons are either identical in structure or that they are completely homogeneous.* It has recently been shown that catalytic hydrogenation of myrcene does not give a pure product (see p. 18), and that dihydromyrcene is not formed in any appreciable quantity by the reduction of *allo*-ocimene.

Dihydromyrcene prepared by the reduction of myrcene† has b.p. 166–168°/761 mm., 62–63°/17 mm., d^{15}_4 0.7802, n^{20}_D 1.4507.

The constitution of dihydromyrcene has been determined by degradation experiments and also by its synthesis.

Enklaar‡ has shown that, when the hydrocarbon (I) is oxidised with potassium permanganate, it yields a liquid polyhydroxy derivative (II) which on further oxidation gives acetone, levulinic acid and acetic acid, a degradation explained most simply by the scheme:



With a view to confirming the assignment of formula (I) to dihydromyrcene, Enklaar oxidised the hydrocarbon with ozone, and on decomposition of the resulting ozonides with water,

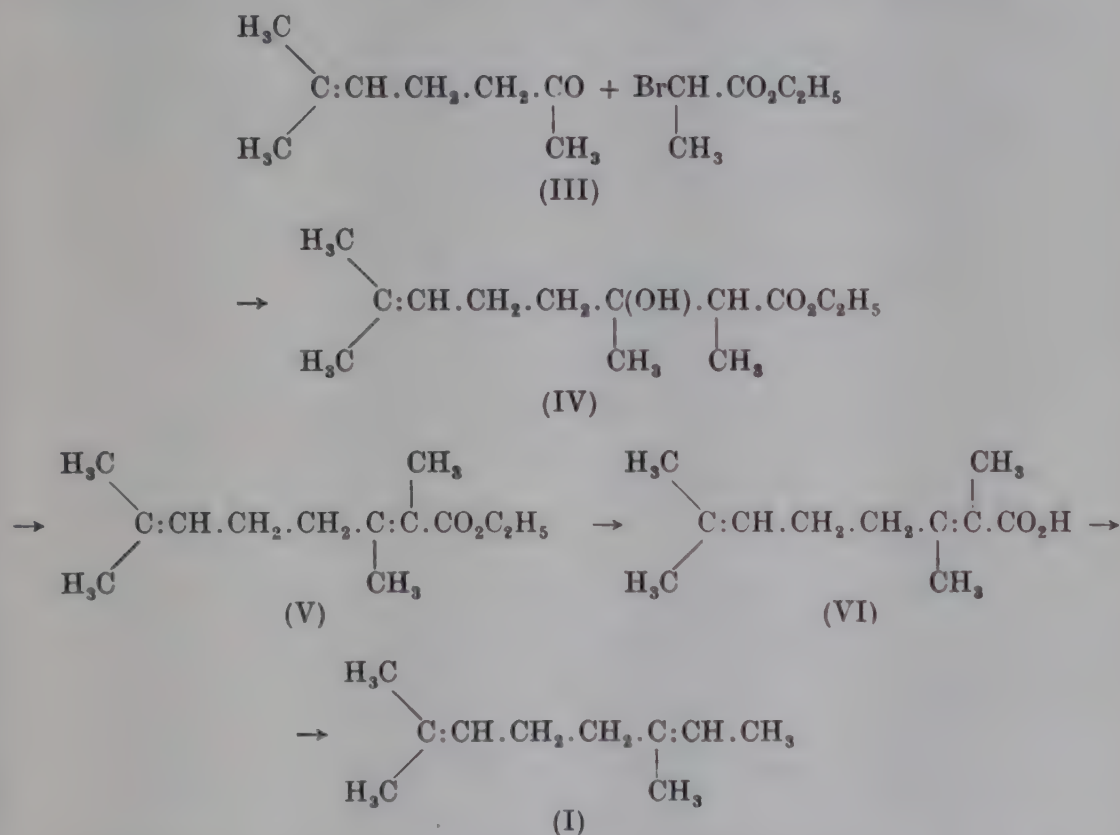
* The hydrocarbon prepared by Forster and Cardwell (*J.C.S.* 1913, **103**, 1343), by treatment of geranyl chloride with zinc dust, and regarded by them as probably identical with dihydromyrcene, has been shown by Phillips (*M.Sc. Thesis*, Bangor 1936) to be a mixture of an acyclic and a monocyclic hydrocarbon of undetermined structure. The crystalline *nitrosate* prepared by Forster and Cardwell is derived from the cyclic hydrocarbon.

† Semmler and Mayer, *Ber.* 1911, **44**, 2010.

‡ *Rec. trav. chim.* 1907, **26**, 157; 1908, **27**, 426.

obtained acetone, acetic acid, levulinic acid and also probably malondialdehyde and levulinaldehyde. It may thus be concluded that the hydrocarbon examined by Enklaar consisted essentially of 2:6-dimethyl- $\Delta^{2:6}$ -octadiene.

In 1908 Tiffeneau* described a synthesis of dihydromyrcene. By the condensation of *methylheptenone* (III) with ethyl α -bromopropionate he prepared the *hydroxy-ester* (IV), which, when dehydrated with acetyl chloride, gave *ethyl 1-methylgeranate* (V). The acid (VI) obtained from this on hydrolysis yielded on distillation dihydromyrcene (I) by loss of carbon dioxide.

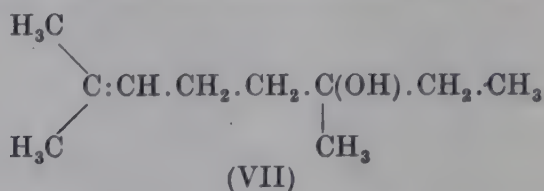


Although this synthesis taken in conjunction with Enklaar's experiments would appear to place the constitution of dihydromyrcene on an indisputable basis, it is not improbable that it is a mixture of 2:6-dimethyl- $\Delta^{2:6}$ -octadiene and 2:6-dimethyl- $\Delta^{1:6}$ -octadiene, since the experiments of Grignard and his collaborators† have shown that methylheptenone from natural sources is always a mixture of the $\Delta^{1:6}$ - and $\Delta^{2:6}$ -isomerides, in which the latter isomeride predominates.

* *Compt. rend.* 1908, **146**, 1154.

† *Bull. Soc. chim.* 1924 [iv], **35**, 932.

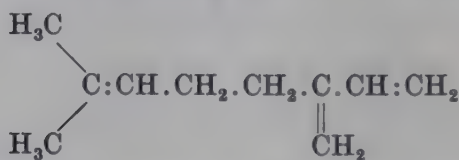
By the action of dilute sulphuric acid in acetic acid solution, dihydromyrcene is converted into cyclodihydromyrcene, the properties of which are discussed on p. 111. If the reaction is allowed to proceed at a low temperature it is, however, possible to separate the *acetate* of dihydrolinalool (VII).*



Farmer and Sutton[†] have shown that hydroxylation occurs, probably in an allyl position, when dihydromyrcene is exposed to oxygen in ultra-violet light, and Bloomfield[‡] has described a *bromodihydromyrcene*, b.p. 54°/0.1 mm., obtained by the action of *N*-bromosuccinimide on the hydrocarbon.

MYRCENE

(2-Methyl-6-methylene- $\Delta^{2:7}$ -octadiene)



Myrcene, $\text{C}_{10}\text{H}_{16}$, was isolated by Power and Kleber[§] from the essential oil obtained from the leaves of *Myrcia acris* D.C. (oil of bay). It has since been found to occur in a number of other essential oils, more especially verbena oil^{||} (from the leaves of *Lippia citriodora*), oil of hops,[¶] the oil from the leaves of *Barosma venusta*,^{**} and that from the seeds of *Zanthoxylum ovalifolium*.^{††}

Myrcene is a pleasant-smelling oil, b.p. 166–168°/760 mm., d_{15}^{15} 0.8013, n_D^{19} 1.4700,^{**} λ max. 2245 (Σ , 14600).^{§§} It is much more stable than the isomeric hydrocarbon ocimene (p. 19).

* Schimmel's Report, 1911, Oct. p. 130.

† J.C.S. 1942, p. 139.

‡ J.C.S. 1944, p. 120.

§ Pharm. Rundschau, 1895, 13, 60.

|| Barbier, Bull. Soc. chim. 1901 [iii], 25, 691.

¶ Chapman, J.C.S. 1903, 83, 506; Semmler, Ber. 1911, 44, 2009; Deussen, Annalen, 1912, 388, 146.

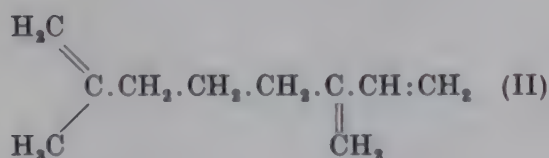
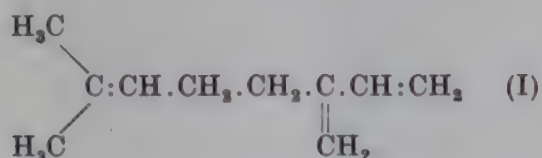
** Goulding and Roberts, J.C.S. 1914, 105, 2614.

†† Simonsen, Ind. For. Rec. 1924, 11, 3.

‡‡ Enklaar, Rec. trav. chim. 1907, 26, 166. Compare Palkin and Wells, J. Amer. C.S. 1933, 55, 1552.

§§ Booker, Evans and Gillam, J.C.S. 1940, p. 1453.

It was suggested by Power and Kleber* that myrcene was an aliphatic hydrocarbon with three ethylenic linkages and that it had the same carbon skeleton as linalool. They based the latter conclusion on the fact that when myrcene was hydrated with sulphuric acid in acetic acid solution at 40°, an alcohol was formed which they regarded as identical with linalool, since on oxidation it gave citral, the latter being identified by the preparation of its derivative, *citryl β-naphthocinchoninic acid*. These authors further observed that on oxidation myrcene gave succinic acid. In 1901 Barbier† reinvestigated the hydration of myrcene and, working at room temperature instead of at 40°, he obtained an alcohol which was not identical with linalool and to which he gave the name *myrcenol* (p. 68). In the same year Semmler‡ showed that, when myrcene was reduced with sodium and alcohol, a hydrocarbon, dihydromyrcene (p. 9), of the formula $C_{10}H_{18}$, was formed, only two atoms of hydrogen being taken up. This led him to suggest that in myrcene two of the ethylenic linkages were conjugated, a view supported by the fact that on bromination myrcene only takes up four atoms of bromine. Correlation of these experiments with those of Power and Kleber led Semmler to suggest that myrcene was represented by either formula (I) or (II).



Ruzicka and Stoll§ have shown conclusively that formula (I) correctly represents myrcene. They subjected the hydrocarbon to oxidation with ozone and, after decomposition of the ozonide and further treatment with chromic acid and sodium hypobromite, they obtained as the sole product of the reactions

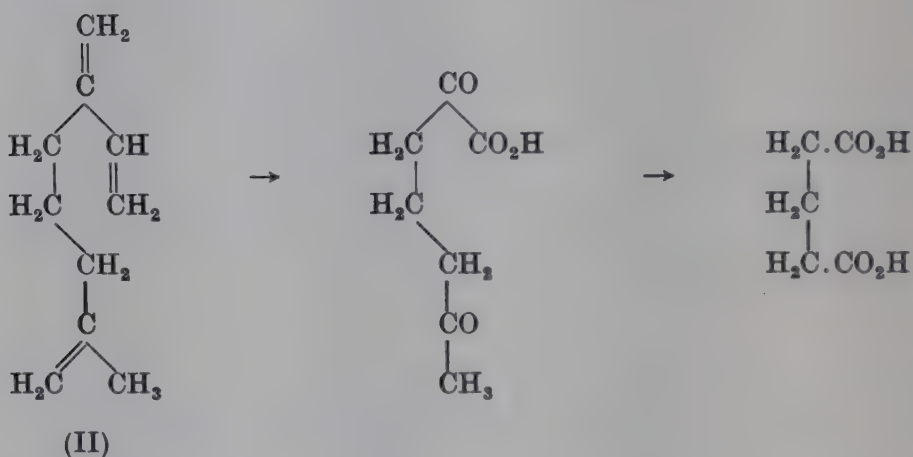
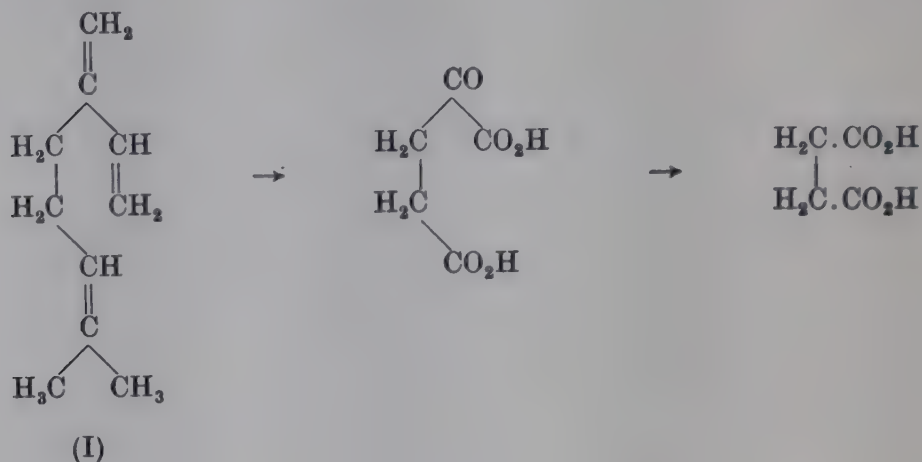
* *Pharm. Rundschau*, 1895, 13, 60.

† *Ber.* 1901, 34, 3126.

‡ *Bull. Soc. chim.* 1901 [iii], 25, 691.

§ *Helv. Chim. Acta*, 1924, 7, 272.

succinic acid. If the hydrocarbon had formula (II), the formation of glutaric acid would have been anticipated, as will be clear from the schematic representation given below:

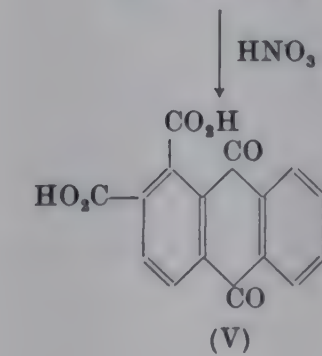
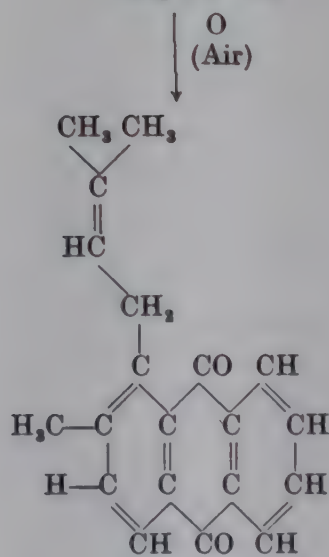
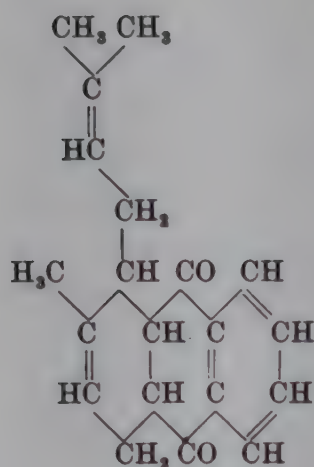
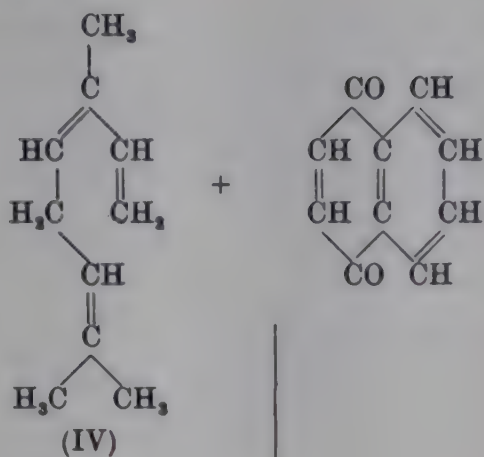
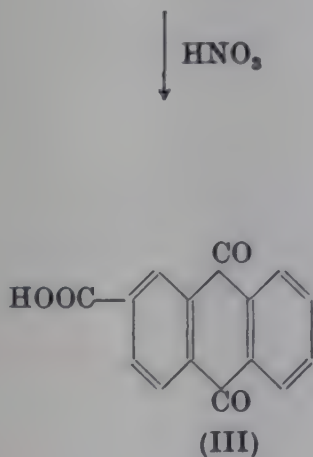
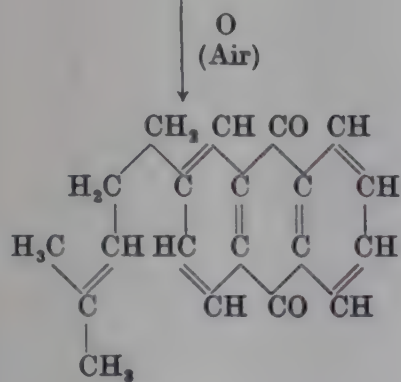
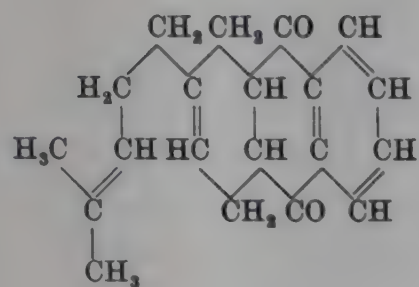
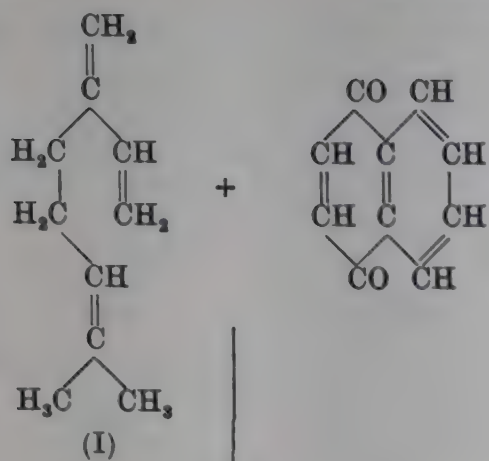


Myrcene has not been prepared by any direct synthesis but, according to Enklaar,* it is formed when linalool is passed over activated copper at 130–140° and also by treatment of the alcohol with phenylisocyanate. Arbusow and Abramow† performed the dehydration with a trace of iodine, and confirmed the structure of their product by condensation with α -naphthaquinone,‡ and oxidation of the adduct to the *anthraquinone monocarboxylic acid* (III). The alternative product (IV) would have given the *dicarboxylic acid* (V).

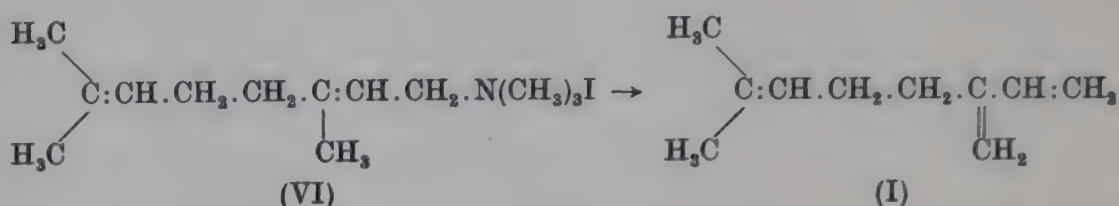
* *Chem. Weekblad*, 1912, **9**, 68.

† *Ber.* 1934, **67**, 1942.

‡ Compare Diels and Alder, *Annalen*, 1929, **470**, 65; *Ber.* 1929, **62**, 2337.



Myrcene is obtained in 70 per cent. yield by the pyrolysis of β -pinene under the conditions described by Goldblatt and Palkin,* and it has been prepared also by Mannich, Handke and Roth† by distillation of the *methiodide* of dimethylgeranylamine (VI).



Myrcene, although much more stable than ocimene, is still highly reactive. Ostromisslensky‡ has shown that on pyrogenetic depolymerisation isoprene is formed in high yield. The polymerisation of myrcene has led to results of considerable interest. Many years ago Harries§ showed that, when myrcene was heated in a sealed tube at 300°, it gave an oil, b.p. 160–200°/12–16 mm., to which he gave the name *dimyrcene*, together with a viscid gum, *polymyrcene*. He characterised dimyrcene by the preparation of a crystalline nitrosite which he considered to be identical with a nitrosite prepared by him from rubber. Dimyrcene has been studied by Semmler and Jonas,|| who have shown it to be a mixture of hydrocarbons from which they separated a sesquiterpene, α -camphorene, which occurs in blue camphor oil. Since this hydrocarbon is readily characterised through its crystalline *trihydrochloride*, these authors¶ have suggested that the polymerisation of myrcene to α -camphorene might prove to be a convenient method of identification when the aliphatic hydrocarbon was present in an essential oil in small amount. The structure of the substance which they termed *cycloisoprene myrcene*, obtained by the interaction of isoprene and myrcene at 225°, has been elucidated by Ruzicka and Bosch.** They have

* *J. Amer. C.S.* 1941, **63**, 3517.

† *Ber.* 1936, **69**, 2112.

‡ *J. Russ. Phys. Chem. Soc.* 1915, **47**, 1947.

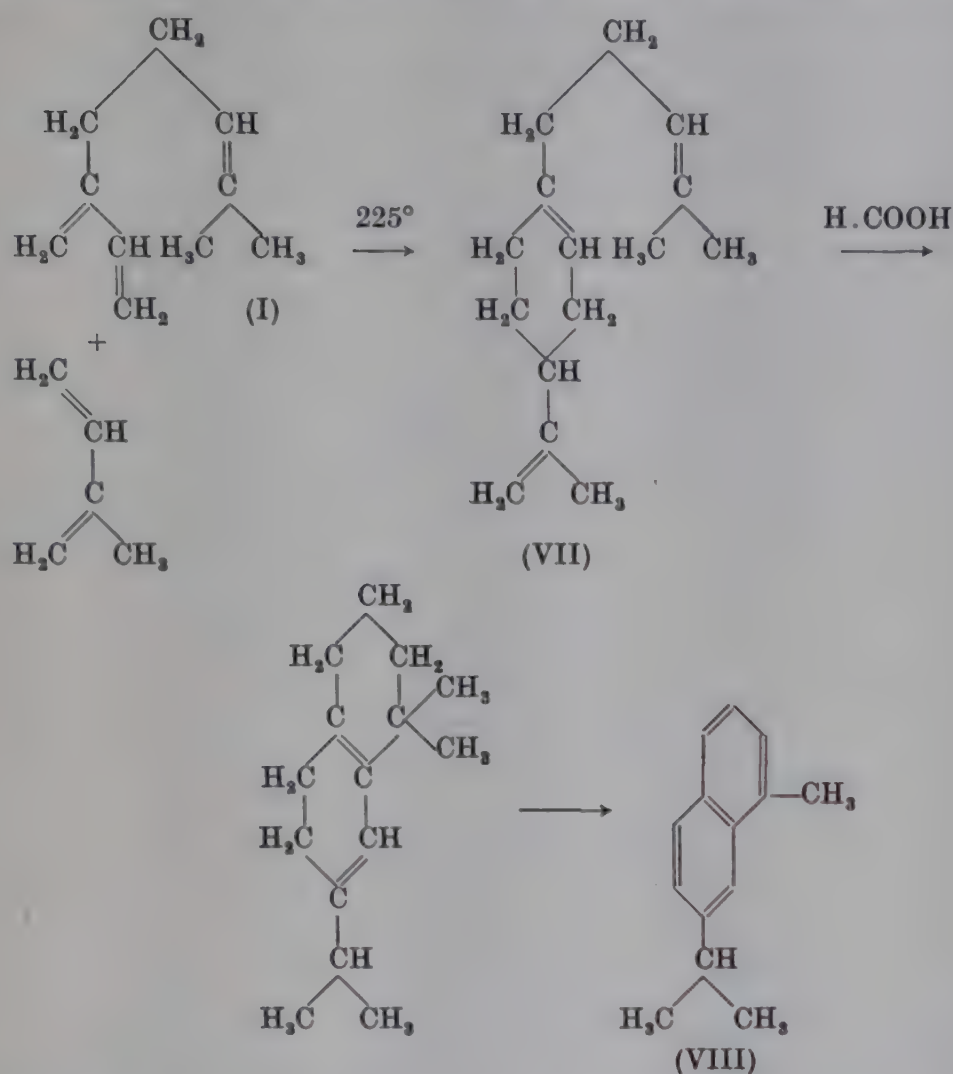
§ *Ber.* 1902, **35**, 3259; compare Runckel and Goldblatt, *Ind. Eng. Chem.* 1946, **38**, 749.

|| *Ibid.* 1913, **46**, 1567; compare Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 272; and Kafuku, Oyamada and Nishi, *Bull. Chem. Soc. Japan*, 1933, **8**, 144.

¶ *Ber.* 1914, **47**, 2071.

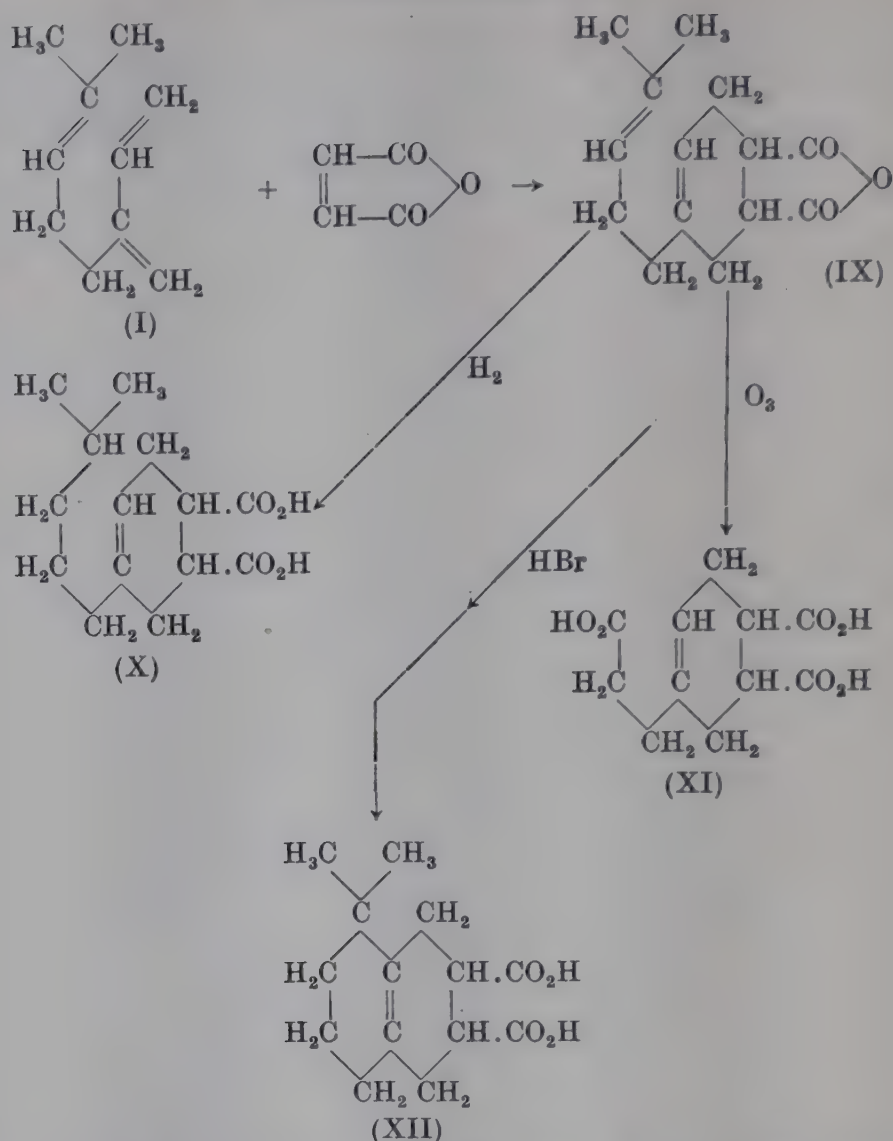
** *Helv. Chim. Acta*, 1931, **14**, 1336.

shown it to be represented by (VII). On cyclisation with formic acid, followed by dehydrogenation, it yields *eudalene* (VIII):



Diels and Alder,* by condensing myrcene with maleic anhydride, have prepared the *anhydride* of *cis*-4-*isohexenyl*- Δ^4 -*cyclohexene*-1:2-*dicarboxylic acid* (IX), m.p. $34-35^\circ$, b.p. $202-206^\circ/12\text{ mm.}$, from which the *acid*, m.p. $122-123^\circ$, can readily be obtained. On hydrogenation in the presence of a palladium catalyst, the ethylenic linkage in the side chain is reduced with formation of *cis*-4-*isohexyl*- Δ^4 -*cyclohexene*-1:2-*dicarboxylic acid* (X), whilst oxidation with ozone yields the substituted *propionic acid* (XI). When the *cis*-acid (IX) is heated with hydrogen bromide, it undergoes cyclisation with formation of 1:1-*dimethyloctahydronaphthalene*-6:7-*dicarboxylic acid* (XII), m.p. $206-207^\circ$.

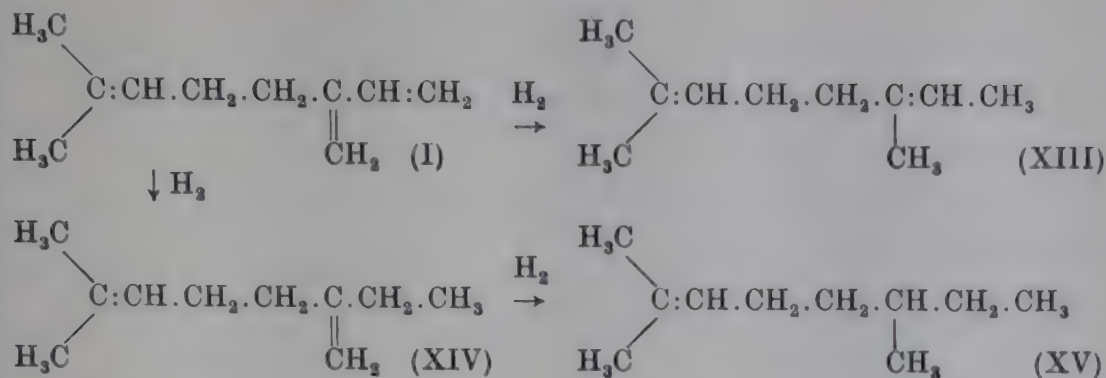
* *Annalen*, 1929, 470, 65.



Mainly on the evidence of Raman spectra, Dupont and Desreux* have shown that, in the catalytic hydrogenation of myrcene, 1:4 addition of hydrogen is accompanied by 1:2 addition. The product is thus a mixture of *dihydromyrcene* (XIII) and 2-methyl-6-ethyl- $\Delta^{2:6}$ -heptadiene (XIV), in proportions which depend upon the nature of the catalyst. The diene (XIV), unlike (XIII), is susceptible to further hydrogenation, and yields *tetrahydromyrcene* (XV), b.p. 65–66°/17 mm., which, according to Mannich, Handke and Roth,[†] gives 2:6-dimethyloctane on prolonged hydrogenation in the presence of a relatively large amount of platinum.

* *Compt. rend.* 1936, **203**, 623, 733; *Bull. Soc. chim.* 1937 [v], **4**, 422. The reliance which can be placed upon the determination of the structure of terpene hydrocarbons by examination of the Raman spectra is discussed on p. 4.

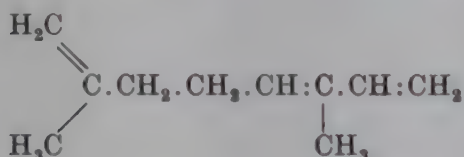
[†] *Loc. cit.*



Delaby and Dupin* have investigated the oxidation of myrcene with selenium dioxide and, from the complex mixture of carbonyl and hydroxy compounds formed, have isolated a *myrcenal*, b.p. 117–119°/17 mm., and a primary alcohol, *myrcenol*, b.p. 123–128°/17 mm., the structures of which have not been determined.

OCIMENE

(2:6-Dimethyl- $\Delta^{1:5:7}$ -octatriene)



Ocimene, $\text{C}_{10}\text{H}_{16}$, was first isolated by van Romburgh† from the oil obtained from the leaves of *Ocimum basilicum* Linn. grown in Java. He described it as a mobile oil, b.p. 176–178° (decomp.), 73–74°/21 mm., d^{22}_4 0.794, n_D 1.4861. Hydrocarbons with similar constants and properties have since been separated from oils from the leaves of *Ocimum gratissimum* Linn.,‡ from the fruits of *Evodia rutaecarpa*,§ and from the leaves of *Homoranthus flavescens*.||

Our knowledge of the chemistry of ocimene is due mainly to the extended investigations of Enklaar.¶ After careful purification the hydrocarbon has b.p. 81°/30 mm., d^{15}_4 0.8031, n_D^{18} 1.4857,

* Bull. Soc. chim. 1938 [v], 5, 931.

† Proc. K. Acad. Wetensch. Amsterdam, 1900, 3, 454.

‡ Roberts, J.S.C.I. 1921, 40, 164 T.

§ Asahina, Acta Phytochim. 1922, 1, 67.

¶ Penfold, J. Proc. Roy. Soc. New South Wales, 1922, 56, 197.

¶ Rec. trav. chim. 1907, 26, 157; 1908, 27, 422; 1917, 36, 215; 1926, 45, 337.

thus showing a marked exaltation in its molecular refraction* ($[R_L]_D$ 53.05, $C_{10}H_{16}$ 46.98). It would, however, appear apparently to be somewhat doubtful if ocimene has ever been obtained quite pure and free from isomerides, more especially from *allo*-ocimene. Ocimene is very readily oxidised, being converted on short exposure to the air into a yellow resin, but in the absence of oxygen it can be preserved unaltered. It does not yield any characteristic crystalline derivatives. When boiled for some hours in a neutral atmosphere it undergoes isomerisation, being converted into a hydrocarbon which is known as *allo-ocimene*, b.p. $81^\circ/12$ mm., d^{16}_4 0.8172, n^{16}_D 1.5296. The two hydrocarbons were originally considered by Enklaar to be stereoisomerides, but his further investigations have shown this view to be untenable.

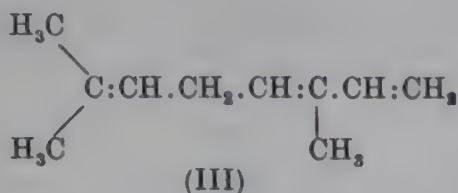
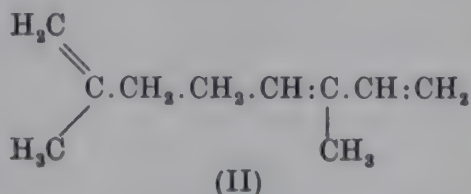
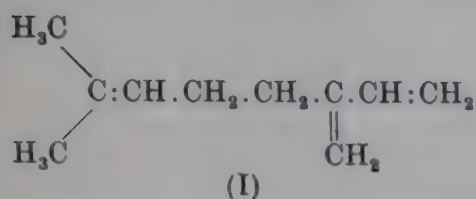
Owing to its instability the determination of the constitution of ocimene has offered considerable difficulty. When ocimene is reduced with sodium and alcohol, it takes up only two atoms of hydrogen with formation of "dihydro-ocimene", indicating that two of the ethylenic linkages are conjugated. Examination of "dihydro-ocimene" has shown it to be identical with the hydrocarbon dihydromyrcene formed by the reduction of myrcene under similar conditions (see p. 9). This identity was established by the conversion of "dihydro-ocimene" into *tetrabromodihydromyrcene*, m.p. $87-88^\circ$.

The oxidation of ocimene with potassium permanganate, either in alkaline or in acetone solution, results in very complete degradation, and is of little aid in the elucidation of the constitution of the hydrocarbon. When the oxidation was carried out in acetone solution, Enklaar noted the formation of acetic and oxalic acids together with a little malonic acid. The products formed on oxidation with ozone were of more direct value, consisting of acetic and malonic acids, trioxymethylene and methylglyoxal, together with a small quantity of acetone.

Since ocimene must contain the same carbon skeleton as myrcene (I) (see p. 12), it follows from the formation of the above-mentioned oxidation products that it is in all probability represented by formula (II), although the presence of acetone

* Compare Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], **82**, 84; **84**, 41; Auwers, *Annalen*, 1918, **415**, 128.

amongst the oxidation products indicates contamination with a small quantity of a hydrocarbon of formula (III).



It is possible that ocimene from some sources contains a higher proportion of (III), since Dupont and Desreux,* on the basis of Raman spectra, stated that a sample examined by them contained none of the *isopropenyl* form (II) and was to be regarded as the *isopropylidene* form (III). Unfortunately, no chemical investigation of this material was reported.

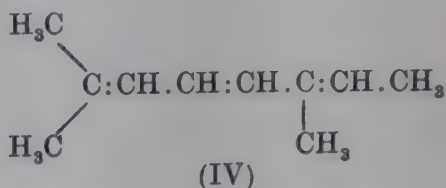
By the hydration of ocimene with a mixture of acetic and sulphuric acids Enklaar† obtained an alcohol, b.p. 97°/10 mm., $d_{15}^{20} 0.901$, $n_D^{15} 1.4900$, to which he gave the name *ocimenol*. This alcohol gave a *phenylurethane*, m.p. 68°, which was not identical with the phenylurethanes prepared from linalool and myrcenol, but it would appear to be doubtful if it is homogeneous. No evidence of its structure is available.

Enklaar has also studied in some detail the properties of *allo-ocimene*. On reduction with sodium and alcohol, a product was obtained which appeared from its physical constants to be *dihydromyrcene*, but which failed to give the characteristic crystalline tetrabromide. Nevertheless, Enklaar considered ocimene and *allo-ocimene* to be stereoisomerides. This was, however, disproved by an examination of the products formed on oxidation with ozone. Unlike ocimene, *allo-ocimene* yielded acetone in considerable quantity but no trioxymethylene was formed; other products of the oxidation were pyruvic acid and the aldehyde of malonic acid. From this it is clear that *allo-ocimene* is best represented by formula (IV), and the

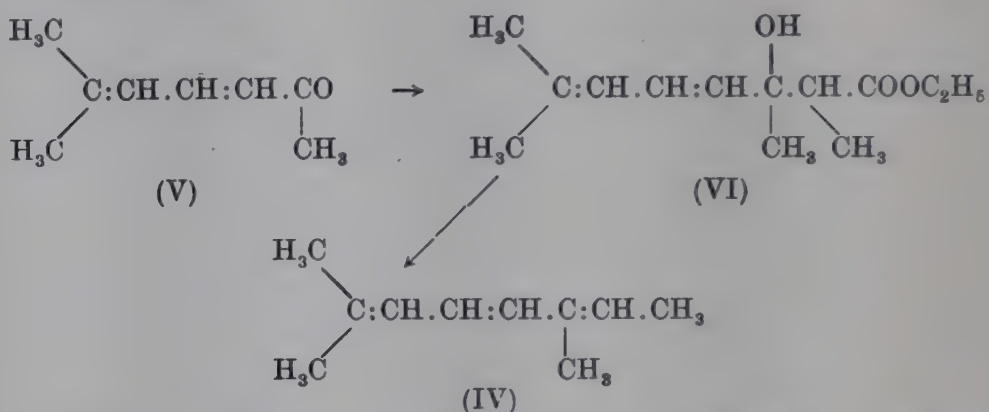
* *Bull. Soc. chim.* 1938 [v], 5, 337.

† *Rec. trav. chim.* 1907, 26, 167.

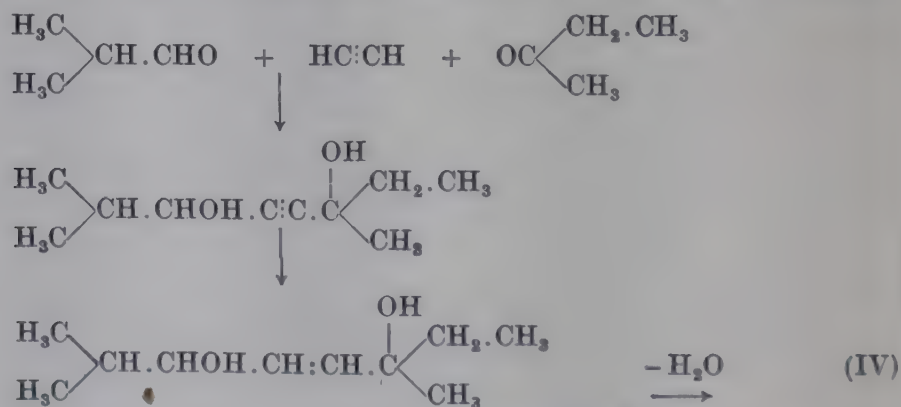
physical constants (especially the molecular refraction) are in good agreement with this.*



This structure is supported by the synthesis described by Fischer and Löwenberg.[†] *Methylheptadienone* (V) undergoes the Reformatsky reaction with α -bromopropionic ester and zinc to give the *hydroxy-ester* (VI); the corresponding acid is dehydrated and decarboxylated by heating under reduced pressure to yield *allo-ocimene* (IV).



A more recent synthesis is due to Lozac'h[‡] who condensed acetylene in the presence of sodamide with methyl ethyl ketone, and then reacted the product with *isobutyraldehyde*. Semihydrogenation of the acetylenic glycol, followed by dehydration, gave *allo-ocimene*, together with other products:



* Auwers and Eisenlohr, *loc. cit.*

‡ *Bull. Soc. chim.* 1941 [v], 8, 519.

† *Ber.* 1933, 66, 669.

Allo-ocimene may now be readily prepared in quantity by the pyrolysis of α -pinene. It was first obtained by this method by Arbusow* in a yield of 25 per cent., and he showed† that the product was identical with the hydrocarbon obtained by isomerisation of ocimene, or by synthesis. By the ozonolysis of the hydrocarbon prepared from α -pinene, Dupont, Dulou, Desreux and Picoux‡ obtained acetone, oxalic acid, formic acid, diacetyl, and methyl acetylcarbinol, in conformity with structure (IV). Arbusow§ claimed that β -pinene also formed *allo-ocimene* on pyrolysis, but this has since been disproved by Goldblatt and Palkin,|| who succeeded, however, in increasing to 40 per cent. the yield from α -pinene. By careful fractionation of *allo-ocimene*, Hopfield, Hall and Goldblatt¶ have separated the hydrocarbon into two constituents: *A*, b.p. $89^\circ/20$ mm., m.p. -21° to -20.6° , d_4^{20} 0.8060, n_D^{20} 1.5446; and *B*, b.p. $91^\circ/20$ mm., m.p. -35.4° to -34.0° , d_4^{20} 0.8118, n_D^{20} 1.5446. These show different Raman spectra, but give the same maleic anhydride adduct, m.p. $83-84^\circ$, and are considered to be stereoisomeric forms. *A* is probably the *trans*- C_4 -*cis*- C_6 , and *B* the *trans*- C_4 -*trans*- C_6 isomer.

Isomerides of the maleic anhydride adduct, and of the corresponding *acid* (m.p. 170°), have been studied by Hultzsch.** No decision has yet been made as to the structures of these products, some of which are probably geometrical isomerides, or of the adducts with naphthoquinone (m.p. 122°), crotonaldehyde, and acrolein, investigated by Arbusow.††

Goldblatt and Palkin** have shown that pyrolysis of *allo-ocimene* at 400° results in the formation of considerable quantities of α - and β -pyronenes (see vol. II, " α -Pinene").

The presence in *allo-ocimene* of three conjugated double bonds suggests that reduction may take place in several ways. Dupont, Dulou, Desreux and Picoux§§ have found that with sodium and

* Ber. 1934, 67, 563.

† Ibid. p. 569.

‡ Bull. Soc. chim. 1938 [v], 5, 322.

§ Trans. Kirov. Inst. Chem. Tech. Kazan. 1935, nos. 4-5, p. 53.

|| J. Amer. C.S. 1941, 63, 3517.

¶ Ibid. 1944, 66, 115.

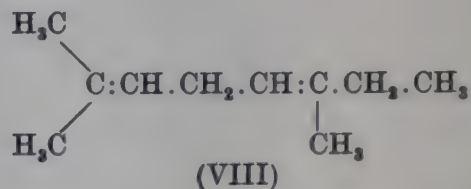
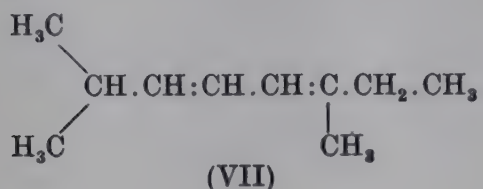
** Ber. 1939, 72, 1173.

†† Loc. cit. and Ber. 1935, 68, 1435.

§§ J. Amer. C.S. 1944, 66, 655.

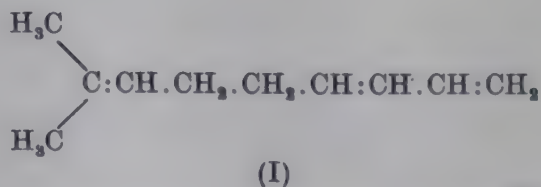
§§ Loc. cit.

liquid ammonia, the sole product is a *dihydro-derivative*, b.p. 57–58°/12 mm., d_{17}^{20} 0.7640, n_D^{20} 1.4684 (maleic anhydride *adduct*, m.p. 158–160°), which is probably 2:6-dimethyl- $\Delta^{3:5}$ -octadiene (VII). This product is obtained also by the use of sodium and alcohol, but is then accompanied by an *isomer*, the physical constants of which (b.p. 59°/12 mm., d_4^{20} 0.7730, n_D^{20} 1.4500) are similar to those of dihydromyrcene.* The Raman spectrum, however, is different from that of dihydromyrcene, and it is considered that the substance is 2:6-dimethyl- $\Delta^{2:5}$ -octadiene (VIII), since it yields acetone and methyl ethyl ketone (identified by Raman spectra) on ozonisation.



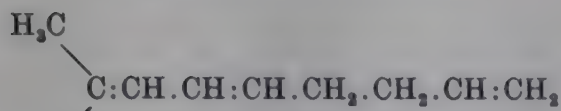
CRYPTOTAENENE

By the distillation in steam of *Cryptotaenia japonica* Hassk., Hirano[†] obtained an essential oil from which an aliphatic terpene, $\text{C}_{10}\text{H}_{16}$, was separated. This hydrocarbon, to which the name *cryptotaenene* has been given, has b.p. 67–68°/15 mm., d_4^{25} 0.8128, n_D^{25} 1.4747, $[\alpha]_D^{19.8}$ +2.66°. It yields a liquid *tetrabromide*, and hence probably contains a conjugated double linkage since it gives on treatment with ozone a *triozonide*, indicating the presence of three ethylenic linkages. Decomposition of the ozonide is stated to yield formic and succinic acids, acetone, acetone peroxide and a carbonyl derivative, the constitution of which was not determined. On the basis of these experiments Hirano suggests that cryptotaenene is represented either by formula (I) or (II).



* Enklaar, *Rec. trav. chim.* 1907, **26**, 174.

† *J. Soc. Chem. Ind. Japan*, 1926, **29**, 48.



(II)

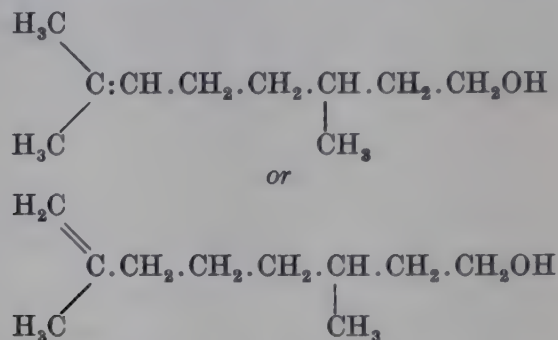
It would appear to be improbable that either of these formulae can be correct, since neither of them is derivable from two molecules of isoprene, nor would they account for the observed optical activity, since they contain no asymmetric carbon atom. A further investigation of this hydrocarbon seems desirable.

CHAPTER II

ALCOHOLS

CITRONELLOL (RHODINOL)

(2:6-Dimethyl- Δ^2 -octen-8-ol or 2:6-Dimethyl- Δ^1 -octen-8-ol)



In 1889 Dodge* prepared by the reduction of the aldehyde citronellal, which he had isolated from citronella oil, an *alcohol*, $\text{C}_{10}\text{H}_{20}\text{O}$, which had a characteristic rose-like smell. At about the same time as these experiments were in progress, a number of other investigators had observed the presence of a new alcohol in the essential oil from *Rosa damascena* Mill. (rose oil) and in that from *Pelargonium odoratissimum* (geranium oil). These two oils resembled one another in smell and they also were like Turkish geranium oil, the main constituent of which had been shown by Semmler to be geraniol (see p. 40).

The oil from *Rosa damascena* was investigated by Eckart† and by Markownikov and Reformatsky.‡ Eckart concluded that rose oil contained an alcohol, $\text{C}_{10}\text{H}_{18}\text{O}$, which was optically active and which differed from geraniol. To this alcohol he gave the name *rhodinol*. Markownikov and Reformatsky, working with Bulgarian rose oil, considered that they had established the presence in it of an optically active alcohol, $\text{C}_{10}\text{H}_{20}\text{O}$, which they called *roseol*. Subsequent investigation has shown that in neither case was the alcohol homogeneous, and in both cases the authors were dealing with mixtures of *l*-citronellol and geraniol.

* *Amer. Chem. J.* 1889, **11**, 463.

† *Arch. Pharm.* 1891, **229**, 355.

‡ *Ber.* 1890, **23**, 3191; *J. pr. Chem.* 1893 [ii], **48**, 293.

The constituents present in rose oil and also in geranium oil were subjected to a detailed investigation by Barbier and his collaborators* and by Hesse.† By fractional distillation the former separated a laevorotatory alcohol, which differed from geraniol, and following Eckart they called it rhodinol, ascribing to it the formula $C_{10}H_{18}O$. Hesse, who purified his alcohol through its hydrogen phthalate, considered that it had either the formula $C_{10}H_{18}O$ or $C_{10}H_{20}O$, and he gave it the name *reuniol*. Wallach and Naschold‡ confirmed the presence of a laevorotatory alcohol, $C_{10}H_{20}O$, in this oil after the appropriate fraction had been freed from geraniol by heating with water for six to eight hours at 200–240° in an autoclave.

The question of the relationship of rhodinol, roseol and reuniol to one another was examined by Bertram and Gildemeister,§ who, by taking advantage of the fact that geraniol forms a compound with calcium chloride, were able to show that all these alcohols were mixtures containing a considerable proportion of geraniol.

Pure citronellol would appear to have been first prepared by Tiemann and Schmidt|| by the reduction of citronellal by Dodge's original method, sodium amalgam in the presence of acetic acid. They purified the alcohol through the hydrogen phthalate and using *d*-citronellal they obtained *d*-citronellol. Attempts to separate the pure alcohol direct from natural sources were made by Barbier and Bouveault¶ and, as already mentioned, by Wallach and Naschold. Barbier and Bouveault decomposed the geraniol by treatment with benzoyl chloride at 140–160°, and both by this and by Wallach's method citronellol of a fair degree of purity can be obtained. A better method of purification was devised by Tiemann and Schmidt,** who found that, on treatment of an ethereal solution of the crude alcohol with phosphorus trichloride, the citronellol could be isolated as a halogenated phosphorus ester soluble in dilute alkali and which, when decomposed by strong alkali, gave pure citronellol. In all cases the citronellol prepared by these authors from rose

* *Compt. rend.* 1893, 117, 177, 1092; 1894, 118, 1154; 119, 281, 334.

† *J. pr. Chem.* 1894 [ii], 50, 472.

‡ *Chem. Zentr.* 1896, I, 809.

§ *J. pr. Chem.* 1894 [ii], 49, 196; 1896 [ii], 53, 225.

|| *Ber.* 1896, 29, 903.

¶ *Compt. rend.* 1896, 122, 530, 673.

** *Ber.* 1896, 29, 922.

oil and geranium oil was laevorotatory, the rotation varying from -4.2° to -1.2° .

Another method for the separation of geraniol and citronellol was advocated by Flatau and Labbé.* After treatment of the mixed alcohols with phthalic anhydride, the mixture of geranyl and citronellyl hydrogen phthalates was dissolved in light petroleum and the solution cooled to -5° , when the geranyl phthalate crystallised, leaving the citronellyl ester in solution. Subsequent investigation† has, however, shown that, although the method is suitable for the preparation of pure geranyl phthalate, the pure citronellyl ester cannot be so obtained.

Contemporaneously with these experiments, the French school under the direction of Barbier‡ continued the investigation of rhodinol and concluded that it was not identical with the *l*-citronellol of Tiemann and his collaborators. Their experiments will be considered later.

Citronellol occurs fairly widely distributed in nature and, in addition to its occurrence in the oils which have already been mentioned, it is found in Ceylon and Java citronella oils, in which it is present in the dextrorotatory form. The following constants have been found for the alcohol derived from natural sources: *d*-citronellol (from Java citronella oil), b.p. $103^\circ/5$ mm., d^{15}_D 0.8604–0.8629, n^{22}_D 1.4565–1.4579, $[\alpha]_D$ $+2.7^\circ$ to $+2.32^\circ$; *l*-citronellol (from geranium oil), b.p. 114 – $115^\circ/12$ mm., d^{22}_D 0.856–0.862, n^{22}_D 1.4561, $[\alpha]_D$ -4.2° .

An animal source of citronellol has recently been reported by Fester, Bertuzzi and Pucci,§ who have shown that it is the main constituent of *yacarovol*, the gland secretion of the alligator.

The question of the constitution of citronellol and rhodinol, which is bound up with the constitution of the corresponding aldehydes, citronellal and rhodinal (see p. 71), has been the subject of a prolonged controversy which still continues. Tiemann, Semmler and their collaborators considered that citronellol was represented by formula (I), whilst Barbier, Bouveault and the French school ascribed to rhodinol this formula and considered citronellol to have formula (II), the two

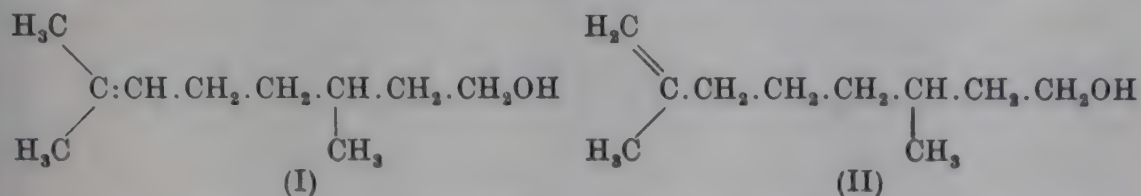
* *Compt. rend.* 1898, **126**, 1725; *Bull. Soc. chim.* 1898 [iii], **19**, 634.

† *Schimmel's Report*, 1898, Oct. p. 59.

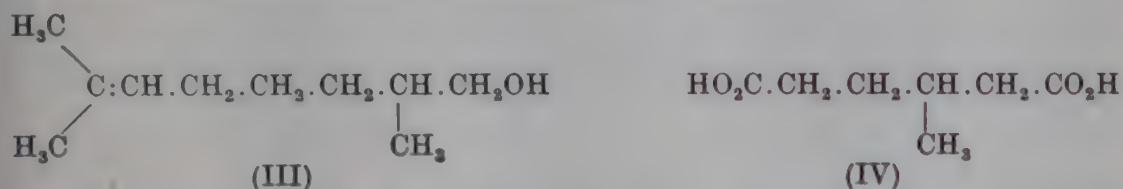
‡ *Compt. rend.* 1896, **122**, 673, 795; *Bull. Soc. chim.* 1900 [iii], **23**, 458.

§ *Ber.* 1937, **70**, 37.

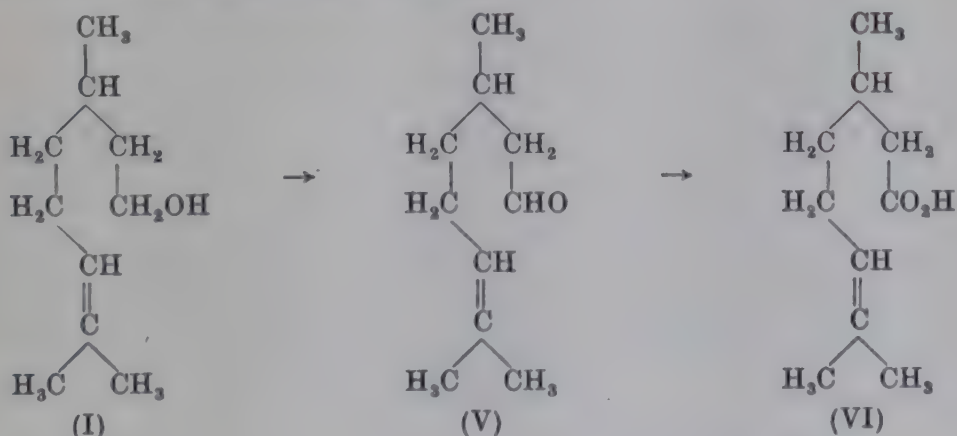
alcohols being structural isomerides. The German chemists, however, regarded them as stereoisomerides, and an attempt will now be made to summarise as briefly as possible the relevant evidence.



It was early recognised that citronellol must be a primary aliphatic alcohol, since it could be prepared by the reduction of the aldehyde citronellal (Dodge, Tiemann and Schmidt), and when it was oxidised with chromic acid mixture it regenerated citronellal which, on further oxidation with silver oxide, gave *citronellic acid*. It had been observed by Semmler* that citronellal on oxidation with chromic acid mixture gave amongst other products an acid which resembled but did not appear to be identical with β -methyladipic acid (IV), and he suggested that citronellol was possibly represented by (III).

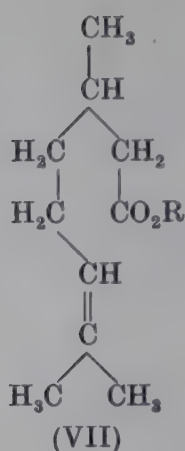


The oxidation of both *d*- and *l*-citronellol with chromic acid was very carefully studied by Tiemann and Schmidt.† They obtained as the products of the reaction *d*- (or *l*-)citronellal (V), *d*- (or *l*-)citronellic acid (VI), the citronellol *ester* of citronellic acid (VII) and *isopulegol* (VIII).

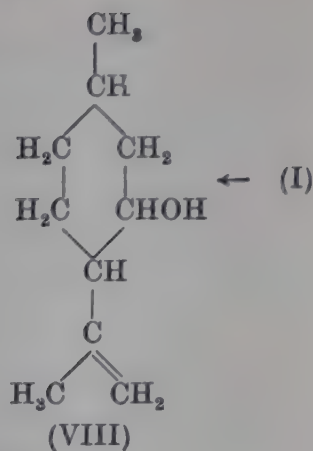


* Ber. 1893, 26, 2254.

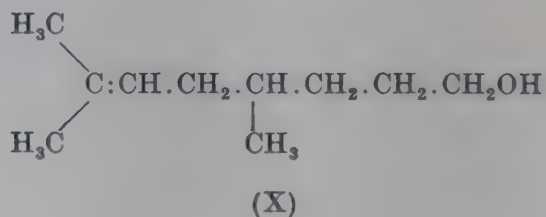
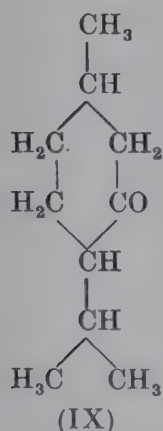
† Ibid. 1897, 30, 32.



(R = citronellyl)

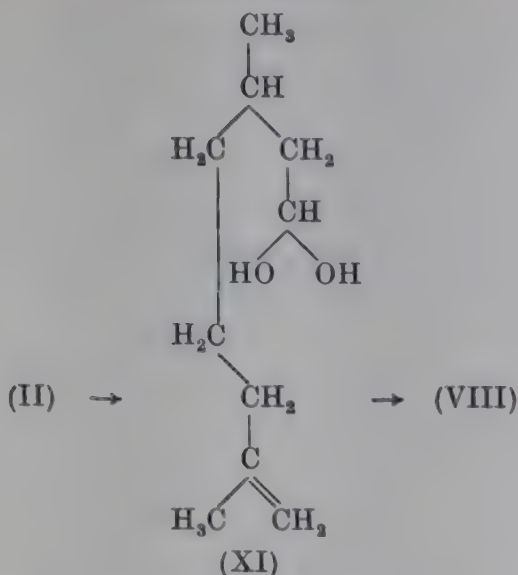


Tiemann and Schmidt showed further that the acid obtained by Semmler, which differed somewhat from β -methyladipic acid, was the optically active form of this acid. By the oxidation of rhodinol, Barbier and Bouveault* obtained similar products, *rhodinal* and *rhodinolic acid*, whilst in addition, in place of *isopulegol*, they isolated an optically active *menthone*. They regarded the formation of menthone† (IX) as very strong evidence in favour of their view that rhodinol was represented by formula (I), although they suggested (X) as a possible alternative.

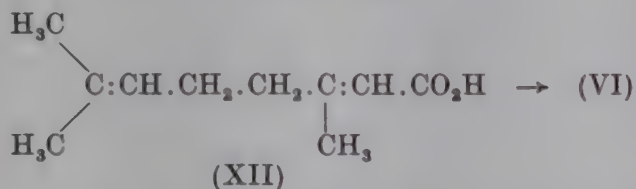


The formation of *isopulegol*, the constitution of which was already established, from citronellol they considered to afford further evidence that citronellol had formula (II), the cyclic alcohol being formed through the intermediate body (XI).

* *Compt. rend.* 1896, 122, 737.† Compare also Bouveault, *Bull. Soc. chim.* 1900 [iii], 23, 463.



The alternative formula (X) was almost immediately shown by Tiemann* to be incorrect, since he found that *geranic acid*[†] (XII), the constitution of which had been established by its synthesis,[‡] on reduction with sodium and alcohol gave an acid identical with *dl*-citronellic acid (VI).



These synthetical experiments were extended by Bouveault and his collaborators[§] who, by the reduction of ethyl geranate with sodium and alcohol, obtained *dl*-rhodinol.

Mention is conveniently made here of the synthetical experiments of Barbier and Locquin,^{||} although they belong to a later date. They suggested that a definite proof of the relationship of citronellol to rhodinol would lie in the conversion of the one into the other. They treated the acetyl derivative of *d*-citronellol (XIII) (prepared from citronellal) with hydrogen bromide in acetic acid solution and obtained the *bromide* (XIV). This substance on removal of the halogen acid by sodium acetate followed

* Ber. 1898, 31, 2901.

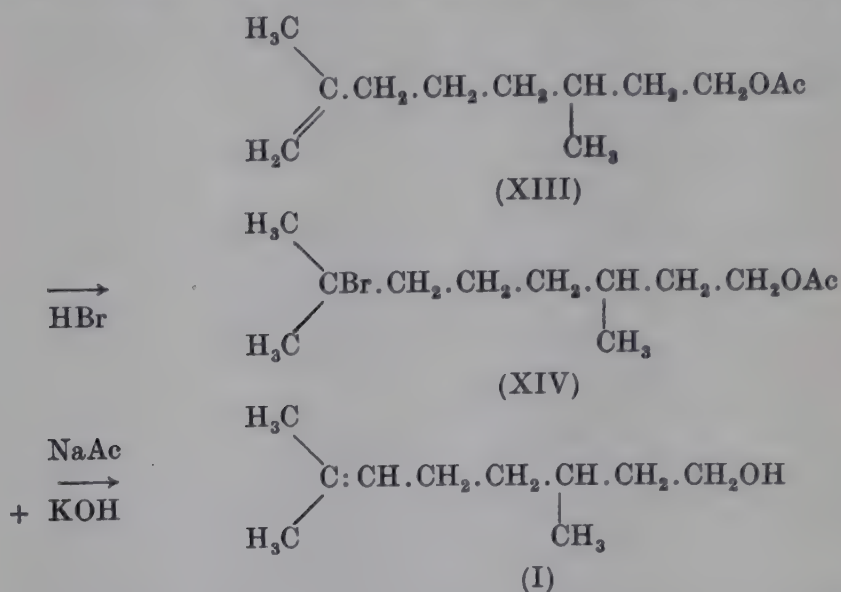
† The natural occurrence of geranic acid has been reported by Glichitch and Naves (*Parfums de France*, 1929, 7, 65) and by Penfold, Ramage and Simonsen (*J. Proc. Roy. Soc. New South Wales*, 1935, 68, 80).

‡ Ber. 1898, 31, 818.

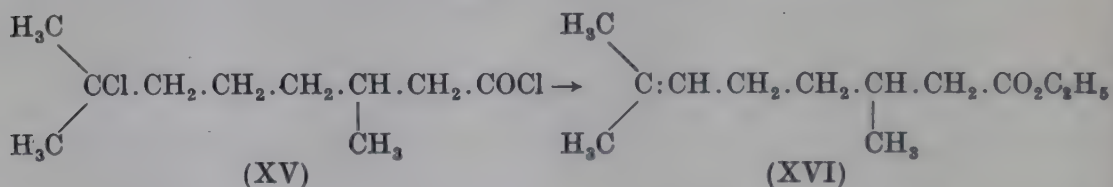
§ Bull. Soc. chim. 1900 [iii], 23, 458; *Compt. rend.* 1904, 138, 1699.

|| *Compt. rend.* 1913, 157, 1114.

by hydrolysis gave *d*-rhodinol, which was stated to have all the properties of the natural alcohol from rose and geranium oils.



d-Rhodinol was also prepared from *d*-citronellal by the following series of reactions. The aldehyde was converted into *d*-citronellic acid (VI) through the oxime and nitrile, and the acid chloride treated with hydrogen chloride, when (XV) was obtained which, after esterification, yielded, on treatment with sodium acetate, *d*-ethyl rhodinate (XVI). Reduction of this ester by the Bouveault method gave *d*-rhodinol.

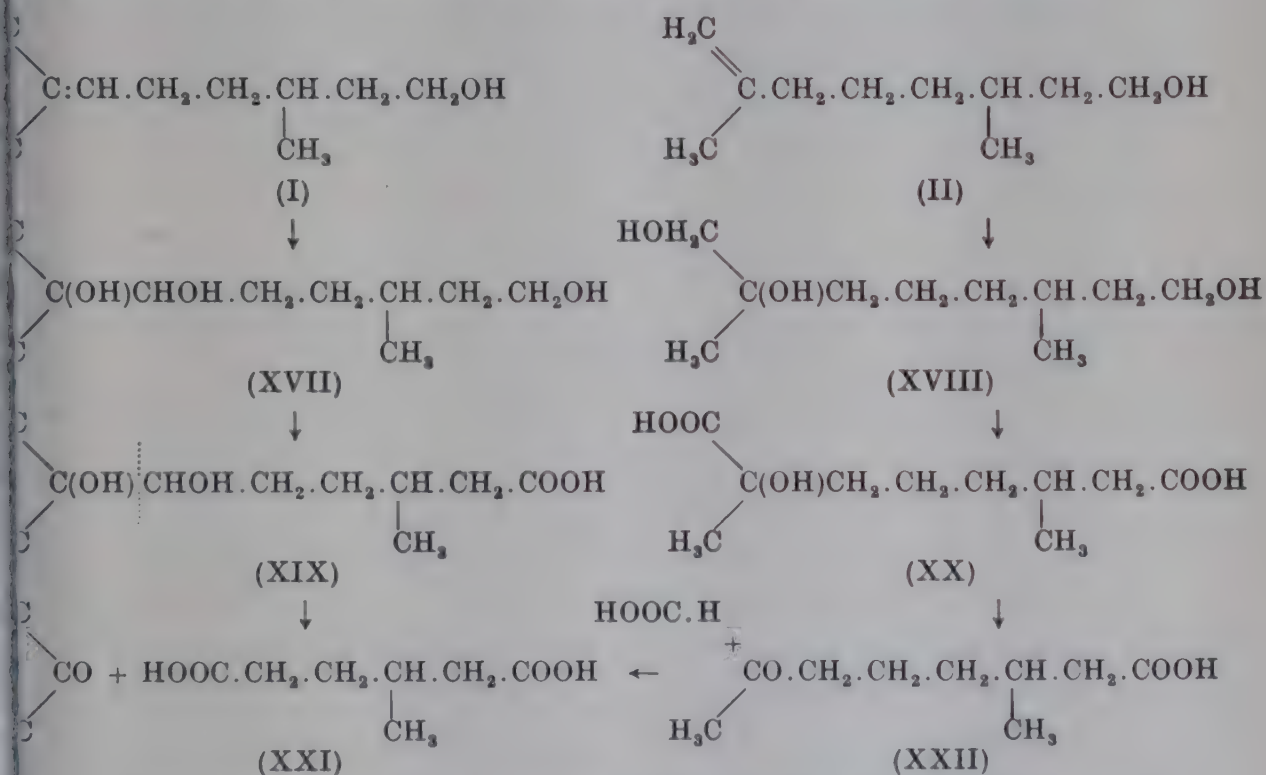


Barbier and Locquin draw particular attention to the marked difference in smell between citronellol and rhodinol. Interesting as these experiments are, they cannot be regarded as conclusive proof of the constitution of either alcohol, since elimination of the halogen acid is unlikely to proceed solely in one direction.

The oxidation of citronellol with potassium permanganate has yielded results of considerable value in the elucidation of the constitution of the alcohol. Tiemann and Semmler* observed that, when the alcohol was oxidised with a 1 per cent. solution of potassium permanganate followed by chromic acid mixture,

* *Ber.* 1895, 28, 2129.

acetone was always found amongst the oxidation products, a fact which they regarded as evidence in favour of formula (I). Wallach,* who oxidised reünol with potassium permanganate, obtained a *glycerol* (b.p. 195°/20 mm.) which, on further oxidation, gave β -methyladipic acid and a liquid acid which very readily lost formic acid on warming. With the object of deciding between formulae (I) and (II) Kötze and Steche† studied with great care the oxidation of citronellol. They treated the alcohol with benzoylhydroperoxide and obtained in this manner, after hydration of the oxide, a *glycerol*, probably identical with that prepared by Wallach, which must be represented either by formula (XVII) or (XVIII), depending upon whether it was derived from (I) or (II). In order to decide between these two formulae, Kötze and Steche studied the intermediate acids formed when this *glycerol* was oxidised with potassium permanganate under carefully regulated conditions. The possible products of the reaction are shown in the following scheme:



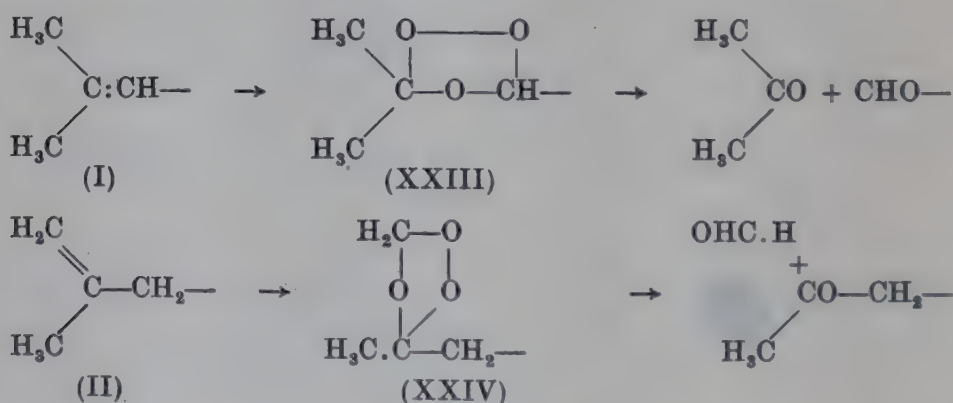
Consideration of the above scheme shows that although both formulae for the alcohol would yield as the ultimate degradation product β -methyladipic acid (XXI), yet the intermediate acids

* *Chem. Zentr.* 1896, I, 809.

† *J. pr. Chem.* 1924 [ii], 107, 197.

(XIX) and (XX) should differ in properties and it might be anticipated that an acid possessing formula (XX) would readily lose formic acid on warming. Kötze and Steche found that a dibasic *hydroxy-acid* (XX) was formed which, on warming under diminished pressure, readily decomposed with liberation of formic acid. They were unable to separate the expected *ketonic acid* (XXII) in a pure state, although a small quantity of a crystalline *phenylhydrazone* was obtained. In addition to the above-mentioned ketonic acid, a small amount of acetone was also separated and Kötze and Steche conclude from their experiments that citronellol is a mixture of the two alcohols possessing formulae (I) and (II), the latter apparently being present in greater quantity.

Confirmation of the view that the alcohols citronellol and rhodinol are identical and are mixtures, in varying proportions of (I) and (II), has been furnished by a study of the oxidation products resulting from the action of ozone. Harries and Himmelmann,* who first studied this reaction, showed that both acetone and formaldehyde were obtained on decomposition of the ozonides, the course of the reaction being indicated by the partial formulae (XXIII) and (XXIV).



Grignard and Dœuvre† have studied the action of ozone on citronellol and rhodinol with great care. *d*-Citronellol was prepared in three different ways: (i) directly from Java citronella oil, (ii) by the reduction of *d*-citronellal, and (iii) by the reduction of the acetyl derivative of the enolic form of *d*-citronellal (see p. 80). They also prepared (iv) *dl*-citronellol synthetically from

* Ber. 1908, **41**, 2187; compare Harries, *Annalen*, 1915, **410**, 8.

† Compt. rend. 1928, **187**, 270, 330; Dœuvre, *Bull. Soc. chim.* 1929 [iv], **45**, 352.

methylheptenyl bromide. Each alcohol was found to be a mixture in which the alcohol represented by formula (I) largely predominated. The percentage composition as calculated from the yields of acetone and formaldehyde is as follows for the different samples referred to above:

	Formula (I)	Formula (II)
	%	%
(i)	80	24
(ii)	81	18
(iii)	76	22
(iv)	76 (72)	25 (28)

For the preparation of rhodinol free from geraniol, they adopted the method of Barbier and Bouveault (treatment with benzoyl chloride at 150°) and that of Tiemann and Schmidt (treatment with phthalic anhydride at 150°). The rhodinol prepared by these methods had very similar properties: (i) b.p. 118–119.5°/18 mm., $d_{15}^{15^\circ}$ 0.860, $n_D^{15^\circ}$ 1.4574, $\alpha_D^{17^\circ}$ +1.52°; (ii) b.p. 117–118.5°/17 mm., $d_{15}^{15^\circ}$ 0.864, $n_D^{15.5^\circ}$ 1.4601. Each alcohol gave a crystalline *allophanate* which was apparently homogeneous and melted at 104–105°. As before, ozonolysis showed that the alcohol was a mixture.

	Formula (I)	Formula (II)
	%	%
(i)	45	53
(ii)	71	25

Substantially the same results have been obtained also by Dœuvre* in a further investigation on rhodinol isolated either from rose oil or geranium oil.

These experiments, which appear to have been carried out with great care, seem to leave no doubt that the two alcohols, citronellol and rhodinol, are identical, both being mixtures of the two alcohols represented by formulae (I) and (II). In only one case does the percentage of that represented by (II) predominate, namely, in the sample of rhodinol prepared by removal of geraniol with benzoyl chloride. A comparative experiment showed that benzoyl chloride causes a partial shift of the ethylenic linkage, since a sample of citronellol containing 24 per cent. of (II) after heating with benzoyl chloride was found to contain 39 per cent., although no change was observed in the

* *Parfums de France*, 1934, 12, 197.

physical properties and the rotatory power was quite unchanged. These results have been confirmed by Escourrou,* who prepared citronellol by the catalytic reduction of geraniol. As the result of experiments on the constitution of citronellal and rhodinol (see p. 74) Verley† considers, however, that citronellol and rhodinol are not mixtures but that the two alcohols can exist as homogeneous substances. He explains the results of Grignard and his collaborators by suggesting that during the ozonolysis a wandering of the ethylenic linkage occurs and so leads to erroneous conclusions. This possibility was considered by Harries,‡ who concluded from his experiments that the change, if it did occur, did so to a very small extent.

Savard,§ from an investigation of the absorption spectrum in the ultra-violet of rhodinol and citronellol, concludes that these are actually different substances, whereas Naves, Brus and Allard|| consider that rhodinol from geranium oil, and citronellol prepared by the reduction of ethyl citronellate, are mixtures of both forms; citronellol prepared by the reduction of citronellal, however, is said to be entirely the Δ^2 -form.

Summing up the evidence, it would seem that Grignard and Dœuvre's conclusions must be accepted, more especially since they agree with the conclusions reached by Kötz and Steche as the result of their experiments on the oxidation of the alcohol with potassium permanganate.

Mention has already been made of the synthesis of citronellol by the reduction of ethyl geranate (p. 31) and from citronellal either by reduction (pp. 27, 29) or through the oxime (p. 32). It has also been obtained by the partial hydrogenation of geraniol in the presence of a catalyst (p. 47) and by the reduction of this alcohol with sodium. It is stated to be prepared technically by the reduction of geraniol with aluminium amalgam.¶ Grignard and Dœuvre** have described its synthesis from methylheptenyl bromide by the use of the Grignard reagent.††

* *Bull. Soc. chim.* 1928 [iv], **43**, 1098.

† *Ibid.* 1924 [iv], **35**, 609; 1928 [iv], **43**, 845; compare Grignard and Dœuvre, *ibid.* 1929 [iv], **45**, 809.

* *Annalen*, 1915, **410**, 8.

§ *Bull. Soc. chim.* 1929 [iv], **45**, 398; compare Dœuvre, *ibid.* pp. 403, 1098.

|| *Compt. rend.* 1935, **200**, 1112.

¶ Ullmann, *Enzyklopädie der Technischen Chemie*, **9**, 573.

** *Compt. rend.* 1928, **187**, 270, 330; Dœuvre, *Bull. Soc. chim.* 1929 [iv], **45**, 352.

†† Compare *Farbenfabr. vorm. F. Bayer, G.P.* 423544.

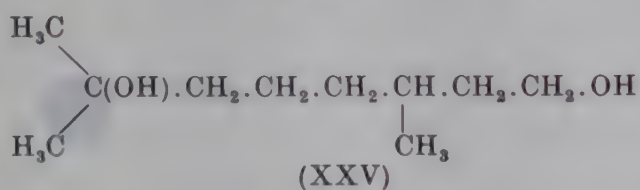
According to Grignard and Dœuvre* citronellol can be most readily characterised by the preparation of the *allophanate*,† m.p. 105–106°, whilst the *semicarbazone* of the *citronellyl* ester of pyruvic acid has been recommended by Bouveault and Gourmand.‡ *Citronellyl hydrogen phthalate* yields a crystalline *silver salt*, m.p. 125–126°. With sodium bisulphite§ citronellol gives a crystalline but extremely hygroscopic compound $C_{10}H_{20}ONaHSO_3$.

When citronellol is reduced with hydrogen in the presence of colloidal platinum or palladium the *decanol*|| is formed and the same product results when the reduction is carried out by the Sabatier-Senderens methods or with Raney nickel.¶ If hydriodic acid is used as the reducing agent, the saturated hydrocarbon, $C_{10}H_{22}$, is obtained.**

The autoxidation of citronellol, which leads to a complex mixture of products, has been studied by Dupont.††

With bromine, citronellol yields a liquid dibromide, whilst it is not acted upon by the halogen acids at the ordinary temperature. On warming with aqueous hydrochloric acid, replacement of the hydroxy group takes place with partial addition to the ethylenic linkage; in acetic acid solution addition only takes place at the double bond, but the products are not stable.

Tiemann and Schmidt** found that, when citronellol was shaken with dilute sulphuric acid, a *glycol* (XXV)§§ was formed, but to



* *Compt. rend.* 1928, **187**, 270, 330; Dœuvre, *Bull. Soc. chim.* 1929 [iv], **45**, 352.

† A mixture of the *d*- and *l*-forms has the same m.p. (Dœuvre, *Compt. rend.* 1939, **208**, 1658; *Bull. Soc. chim.* 1940 [v], **7**, 139).

‡ *Compt. rend.* 1904, **138**, 1699.

§ Labbé, *Bull. Soc. chim.* 1899 [iii], **21**, 1079; Dupont and Labaune, *Sci. Ind. Rep. Roure-Bertrand Fils*, 1913 [iii], **7**, 3.

|| Paal and Amberger, *G.P.* 346949.

¶ Smith, Ungnade, Austin, Pritchard and Opie, *J. Org. Chem.* 1939, **4**, 334; Palfray, *Bull. Soc. chim.* 1940 [v], **7**, 401.

** Markownikov and Reformatsky, *J. pr. Chem.* 1893 [ii], **48**, 299.

†† *Ind. chim. belge*, 1940, **11**, 3.

‡‡ *Ber.* 1896, **29**, 907; see also Barbier and Locquin, *Compt. rend.* 1913, **157**, 1114.

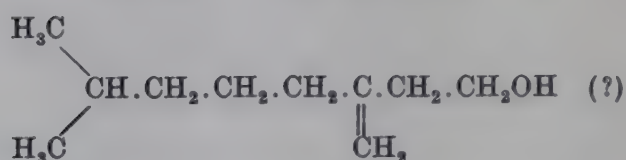
§§ This substance is identical with the 2-hydroxydihydrocitronellol referred to on p. 78.

more concentrated acids it was remarkably stable. It can be mixed with sulphuric acid (50 per cent.) without marked change whilst stronger acids mainly cause polymerisation, the yield of cyclocitronellol being small.

A large number of esters of citronellol have been prepared by interaction with various acids, but these do not call for special comment.

BUPLEUROL

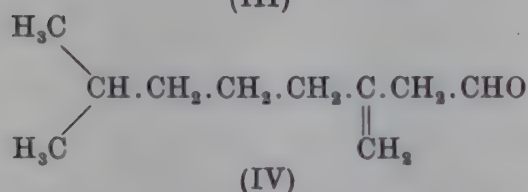
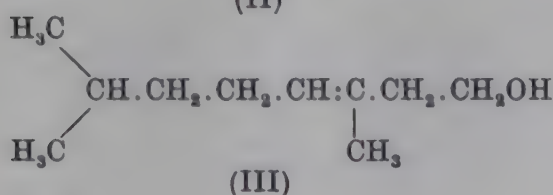
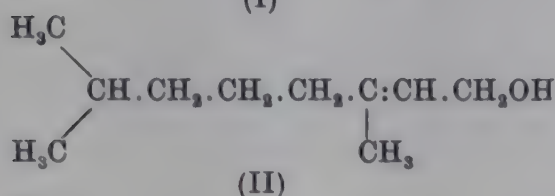
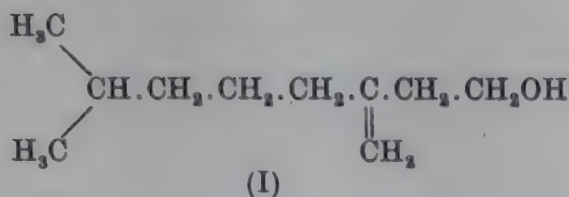
(2-Methyl-6-methylenoctan-8-ol?)



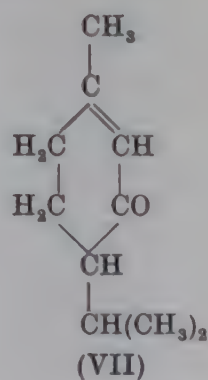
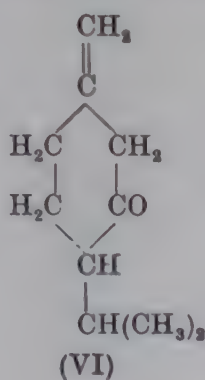
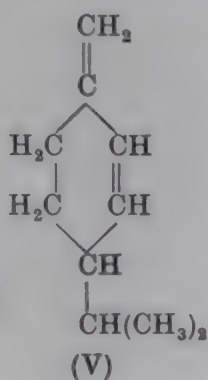
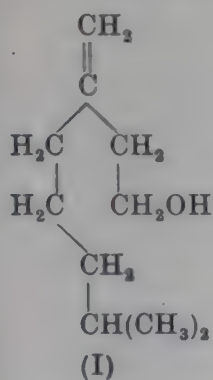
From the essential oil derived from the flowers and leaves of *Bupleurum fruticosum* L., Francesconi and Sernagiotto* separated an alcohol, $\text{C}_{10}\text{H}_{20}\text{O}$, to which they gave the name bupleurol. The alcohol was isolated from the oil by means of its amorphous hydrogen phthalate. It is a colourless liquid with a faint rose-like smell, b.p. $209\text{--}210^\circ/762\text{ mm.}$, d^{17}_D 0.8490, n_D 1.4508, $\alpha_D \pm 0^\circ$. It is most readily characterised by the preparation of the *phenylurethane*, which crystallises from light petroleum in needles, m.p. 45° , and by the crystalline *silver* salt of the hydrogen phthalate which, after purification from a mixture of benzene and methyl alcohol, melts with decomposition at 135° .

The constitution of bupleurol has not been definitely established but, according to Francesconi and Sernagiotto, it is most probably represented by either formulae (I), (II), or (III). It contains one ethylenic linkage, since on treatment with bromine it yields a liquid *dibromide*, whilst, since it is optically inactive, it is unlikely that it contains an asymmetric carbon atom. The presence of a primary alcohol group would appear to be proved by the fact that, on oxidation with chromic acid, it yields an aldehyde, *bupleural* $\text{C}_{10}\text{H}_{18}\text{O}$, the *semicarbazone* of which melts at 135° .

* *Atti R. Accad. Lincei*, 1913 [v], 22, (i) 34, 148. Compare Rutowski, Wino-gradova and Kondratski, *Chem. Zentr.* 1926, i, 1304.



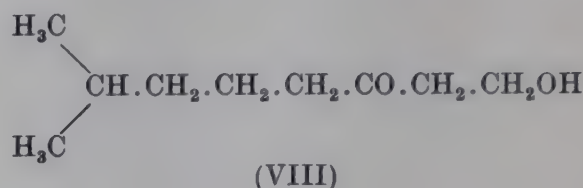
Francesconi and Sernagiotto consider that (I) is the most probable formula for bupleurol, since the other main constituent of the oil is β -phellandrene (V) and the close relationship of (I) to (V) is clear from a consideration of the formulae.



If expression (I) be accepted as a correct representation of the structure of bupleurol, then the aldehyde, bupleural, must have formula (IV). Francesconi and Sernagiotto mention that in addition to bupleural a second aldehyde yielding a semicarbazone, m.p. 97° , and a cyclic ketone, the semicarbazone of which had m.p. $189-190^\circ$, were formed by the oxidation of bupleurol. To the ketone they ascribe formula (VI), but it is not clear whether the second semicarbazone is stereoisomeric with the semicarbazone of bupleural of m.p. 135° or whether it is derived

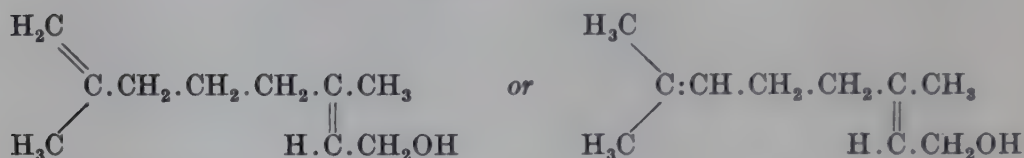
from an isomeric aldehyde. It would appear somewhat improbable that a ketone having the structure (VI) would be stable, since it would undoubtedly tend to isomerise to *piperitone* (VII).

The constitution of this isomeride of citronellol is worthy of further study and it should be possible to establish definitely formula (I) by oxidation to the ketone represented by (VIII).



GERANIOL

(cis-2:6-Dimethyl- $\Delta^{1:6}$ -octadien-8-ol or
cis-2:6-Dimethyl- $\Delta^{2:6}$ -octadien-8-ol)



The unsaturated primary alcohol, geraniol, $\text{C}_{10}\text{H}_{18}\text{O}$, was first separated in a pure state by Jacobsen* from Palmarosa oil. This oil, which is derived from the grass *Cymbopogon Martini* Stapf (var. *motia*), is also known as Turkish geranium oil and *Rosha* or *Rusa* grass oil. *C. Martini* occurs very widely distributed in India, but the oil is obtained mainly from the Bombay Presidency and the Central Provinces.†

Geraniol is also found either in the free state or in the form of its esters in a very large number of other essential oils, for a detailed list of which reference must be made elsewhere.‡ According to Bourquelot and§ Bridel, β -geranylglucoside occurs in the leaves of *Pelargonium odorantissimum* and they have

* *Annalen*, 1871, 157, 234.

† Pearson, *Ind. For. Records*, 1916, 5 [vii], 2. *C. Martini* Stapf (var. *motia*) was formerly known as *A. Schoenanthus* Linn. It should not be confused with *C. Martini* Stapf (var. *sofia*) which yields a much less valuable and quite different ginger-grass oil. The botanical relationship of the two grasses is still somewhat obscure.

‡ Gildemeister and Hoffmann, *Die Ätherischen Öle*, 3rd ed. I, 429.

§ *Compt. rend.* 1913, 157, 72.

prepared this glucoside synthetically by allowing emulsin to act upon an aqueous solution of glucose and geraniol.*

Geraniol is most conveniently obtained pure by taking advantage of the fact, first observed by Jacobsen,[†] that it yields a crystalline derivative with calcium chloride which is decomposed by water. It can also be purified, but less conveniently, through its *hydrogen phthalate*, which gives a crystalline silver salt.[‡]

When purified in this manner geraniol is a colourless oil with a rose-like smell; on keeping, especially if exposed to the air, it becomes discoloured and it becomes less fragrant. It has been found to have the following constants: b.p. 229–230°/757 mm., 114–115°/12 mm., d_{15}° 0.883, n_D^{20} 1.4766.

Geraniol is most readily characterised by the preparation of the *diphenylurethane*, m.p. 82°, which was first described by Erdmann and Huth.[§] It also forms a *p-xenylurethane*, m.p. 69°,^{||} and an *allophanate*, m.p. 124°.[¶]

It was early recognised that geraniol was a primary alcohol, since on oxidation it gave an aldehyde,** consisting mainly of *citral a* (p. 84) and an acid, *geranic acid* (p. 31), containing the same number of carbon atoms. It was also found by Tiemann^{††} that the aldehyde, on reduction with sodium amalgam in dilute acetic acid alcohol solution, was reconverted into geraniol. Since citral has been prepared synthetically (p. 87), this constitutes a synthesis of geraniol. The presence of two ethylenic linkages was established by the preparation of a crystalline *tetrabromide*, m.p. 70–71°.^{‡‡} It is interesting to note that, whilst geraniol forms a stable compound, $C_{10}H_{18}O$, $2NaHSO_3$, with sodium bisulphite, the alcohol cannot be regenerated from this compound by treatment with alkali.^{§§}

* Compare Fischer and Fischer, *Ber.* 1910, **43**, 2522; Fischer and Helferich, *Annalen*, 1911, **383**, 76.

† *Annalen*, 1871, **157**, 234.

‡ Flatau and Labbé, *Compt. rend.* 1898, **126**, 1725; *Bull. Soc. chim.* 1898 [v], **19**, 633; Stephan, *J. pr. Chem.* 1899 [ii], **60**, 248.

§ *J. pr. Chem.* 1896 [ii], **53**, 45; 1897 [ii], **56**, 28.

|| Dœuvre and Desmule, *Bull. Soc. chim.* 1936 [v], **3**, 196.

¶ Naves and Grampoloff, *Helv. Chim. Acta*, 1942, **25**, 1500.

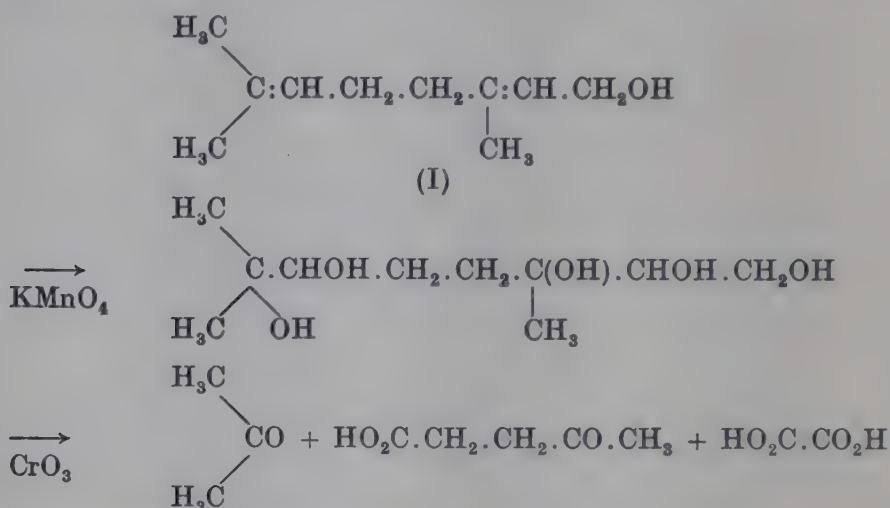
** Semmler, *Ber.* 1890, **23**, 2965; 1891, **24**, 203.

†† *Ibid.* 1898, **31**, 828.

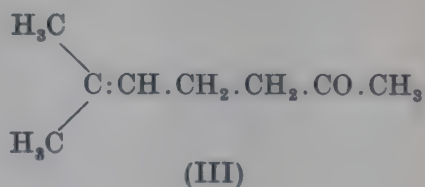
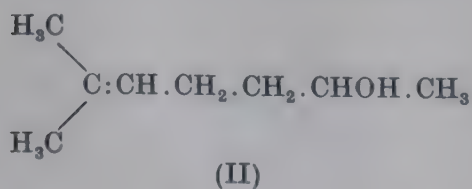
‡‡ Soden and Treff, *ibid.* 1906, **39**, 913.

§§ Labbé, *Bull. Soc. chim.* 1899 [iii], **21**, 1079; Dupont and Labaune, *Sci. Ind. Rep. Roure-Bertrand Fils*, 1913 [iii], **7**, 6.

The first fruitful experiments on the constitution of geraniol were made by Tiemann and Semmler,* who showed that, when the alcohol was oxidised in the cold with potassium permanganate followed by oxidation of the polyhydric alcohol thus obtained with potassium dichromate and sulphuric acid, acetone, levulinic and oxalic acids were formed. They concluded that geraniol was a primary alcohol having the constitution represented by (I), the oxidation proceeding in accordance with the following scheme.



This constitutional formula for geraniol received support from the experiments of Barbier† and Tiemann,‡ who showed that when geraniol was heated with a concentrated alcoholic solution of potassium hydroxide at 150°, *β*-methylheptenol (II) was formed, the structure of which was established by its conversion into *β*-methylheptenone (III) on oxidation. The latter is the primary product of the reaction, being reduced by the alcoholic potassium hydroxide to methylheptenol.



In 1911 Blumann and Zeitschel§ repeated the experiments of Tiemann and Semmler, using a carefully purified specimen of

* Ber. 1895, 28, 2130.

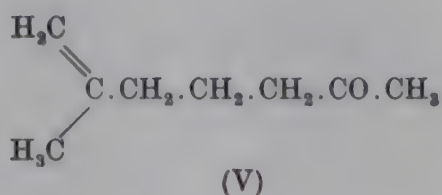
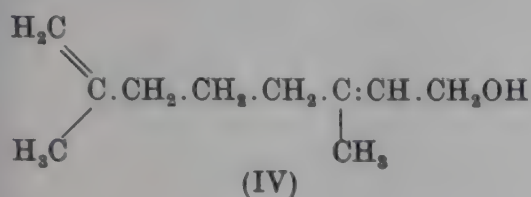
† Compt. rend. 1898, 126, 1423.

§ Ibid. 1911, 44, 2590.

‡ Ber. 1898, 31, 2991.

geraniol prepared from the oil of *Helichrysum angustifolium*. They obtained acetone in a yield of over 50 per cent. of the theoretical and also separated and identified levulinic acid (compare p. 45).

More recently the structure (I) for geraniol has been questioned by Verley,* who has suggested that geraniol is more correctly represented by (IV).



In the course of his early experiments on the constitution of geraniol, Semmler† had observed that, when the alcohol was oxidised with chromic acid mixture, in addition to citral, β -methylheptenone was formed, the constitution of this ketone, b.p. 173–174°, having been established by its synthesis. Verley found that when the two citrals *a* and *b* (p. 86) were digested with dilute alkali, they were both converted into “methylheptenone” but that two distinct ketones were obtained. The ketone from citral *a* had b.p. 168°, whilst that from citral *b* had b.p. 173–174°. The latter was identical with the ketone described by Semmler and is undoubtedly represented by formula (III). The former ketone, which gives no acetone on oxidation, was considered by Verley to have formula (V) and he designated this α -methylheptenone to show the relationship to citral *a*, Semmler’s ketone being called β -methylheptenone. Now it has been clearly established that geraniol on oxidation yields mainly citral *a*, from which Verley deduces that the alcohol must have formula (IV).

In view of these conflicting results the oxidation of geraniol has been the subject of a renewed investigation by Kötz and Steche.‡ Although these authors have not employed any new methods of oxidation, they have so adjusted the conditions of their experiments as to enable them to separate the intermediate products formed. Neither Tiemann and Semmler§ nor Blumann

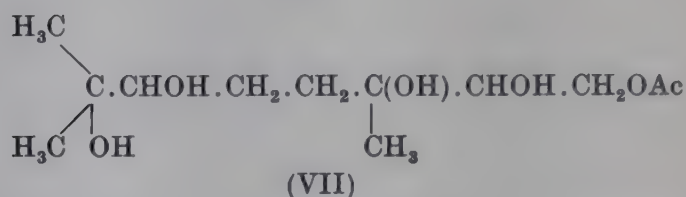
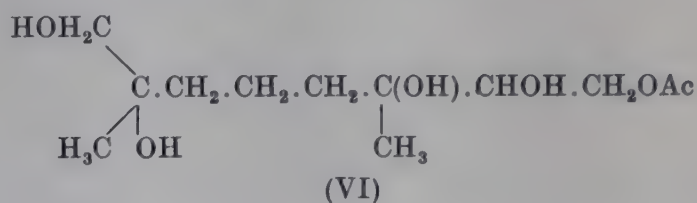
* *Bull. Soc. chim.* 1919 [iv], 25, 68.

‡ *J. pr. Chem.* 1924 [ii], 107, 193.

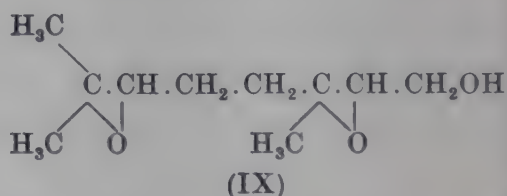
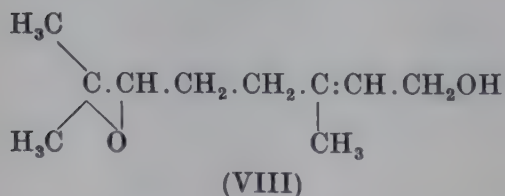
† *Ber.* 1893, 26, 2720.

§ *Ber.* 1895, 28, 2130.

and Zeitschel* attempted to separate in a pure state the primary oxidation product, the polyhydric alcohol, but subjected it immediately to oxidation with chromic acid. Kötze and Steche found that when *geranyl acetate* was oxidised with potassium permanganate in acetone solution, the main product of the reaction (55–60 per cent.) was a crystalline substance, m.p. 106–106.5°. This was not the expected monoacetyl derivative of the pentahydric alcohol (VI) or (VII), but a body containing one molecule of water less.



It was therefore a monoxide derived from either (VI) or (VII). On hydrolysis it gave a crystalline *glycerol oxide*, m.p. 99°. Two substances of a similar structure had been previously obtained by Prileschaev.† This investigator had shown in 1912 that when geraniol was treated with perbenzoic acid, *geraniol monoxide* and *geraniol dioxide* were formed, to which formulae (VIII) and (IX) were assigned.

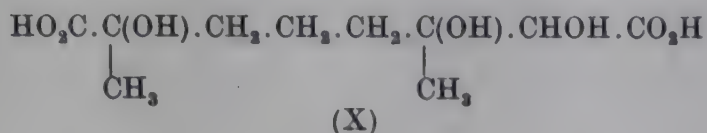


Both these oxides were oils, but from the latter he prepared by the opening of one of the oxide rings two *glycerol monoxides*, m.p. 145–146° and 163–164° respectively. The glycerol monoxide obtained by Kötze and Steche was clearly not identical with either of these but, in view of the number of isomerides which are possible, no attempt was made to determine the relationship.

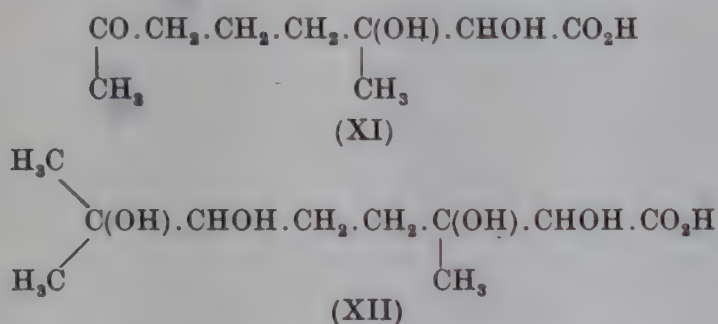
* Ber. 1911, 44, 2590.

† J. Russ. Phys. Chem. Soc. 1912, 44, 613.

When this oxide was oxidised in aqueous solution with dilute potassium permanganate solution, an acid was formed which Kötze and Steche considered to be best represented by formula (X).



This conclusion is based essentially on the fact that the acid was extremely unstable and as soon as it was liberated from its salts formic acid was formed, the decomposition being complete at 40°. Unfortunately it was not found possible to separate in a pure state the *ketonic* acid (XI) which should be formed, although a small quantity of a crystalline *phenylhydrazone* was obtained. An acid having the alternative formula (XII), which might be expected if the glycerol was derived from an alcohol represented by formula (VII), could not yield a ketonic acid by elimination of formic acid.



Kötze and Steche obtained similar results by the oxidation of (a) Prileschaev's dioxide and (b) geraniol itself, when they used six atoms of available oxygen in place of the two used by Tiemann and Semmler.

It will thus be seen that Kötze and Steche's experiments support Verley's* contention that geraniol is 2:6-dimethyl- $\Delta^{1:6}$ -octadien-8-ol, but the results are difficult to interpret in view of the careful experiments of Blumann and Zeitschel which appeared to prove conclusively that one of the ethylenic linkages was in the Δ^2 -position. It would seem to be most probable that geraniol from natural sources is a mixture of the alcohols represented by formulae (I) and (IV), in which either the one or the

* *Bull. Soc. chim.* 1919 [iv], 25, 68.

other form may predominate. This view is supported by the experiments of Grignard and Escourrou,* who have shown that geraniol prepared from citronella oil from Java on oxidation with ozone gives a mixture of formaldehyde and acetone. The percentage of the latter indicated that the oil contained 22.5 per cent. of the alcohol represented by (IV) and 82.5 per cent. of (I). Verley† offers an alternative explanation, namely, that during the oxidation a wandering of the peroxide group takes place similar to that occurring with acyl derivatives. If this should prove to be the case, it would render uncertain much previous work, and evidence for any such reaction seems at present to be very slender.



It should be mentioned that Savard,‡ on the basis of a comparison of the ultra-violet absorption spectrum of geraniol, linalool, citronellol and rhodinol, supports Verley's conclusions,§ whereas Dupont, Desreux and Dulou,|| from an examination of the Raman spectrum of geraniol from Java oil, conclude that the alcohol from this source is entirely free from any Δ^1 -form.

Whether geraniol be regarded as represented by formula (I) or by (IV), or as a mixture of the two, it is obviously possible for it to exist in two stereoisomeric (*cis-trans*-)forms. The alcohol, *nerol* (p. 52) has been shown to be structurally identical with geraniol and it must therefore be stereoisomeric with it. The two alcohols differ very markedly in the rate at which they are converted into α -terpineol by mineral acids, *nerol* reacting very much more rapidly than geraniol. This difference in reactivity is most readily explained by ascribing to geraniol the *cis*-configuration (XIII or XIV) and to *nerol* the *trans*-configuration (XV or XV a).¶

* *Bull. Soc. chim.* 1925 [iv], 37, 542, 546; compare also Grignard and Dœuvre, *ibid.* 1927 [iv], 41, 999; Escourrou, *ibid.* 1928 [iv], 43, 1091, 1211.

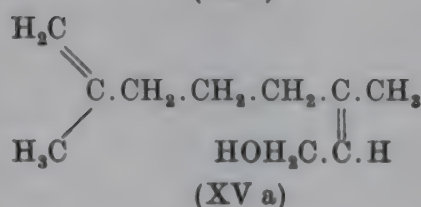
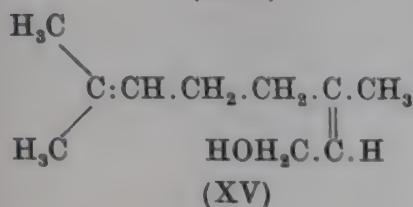
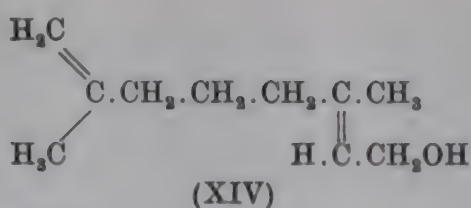
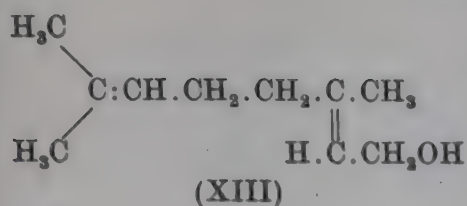
† *Ibid.* 1928 [iv], 43, 854; compare Dœuvre, *ibid.* 1929 [iv], 45, 140, 352.

‡ *Ibid.* 1929 [iv], 45, 398.

§ Compare p. 36.

|| *Bull. Soc. chim.* 1937 [v], 4, 2016.

¶ The prefix *cis* or *trans* is used here with reference to the relative positions of the methyl and hydroxymethyl groups to one another, a convention which is not universally applied.



Reference has already been made to the fact that the formation of geraniol by the reduction of citral constitutes a synthesis of the alcohol, since citral has been prepared synthetically (p. 87). A second indirect synthesis is implied in the conversion of linalool into geraniol, since the former alcohol has been obtained synthetically (p. 61). This change is brought about by the digestion of linalool with acetic anhydride, when, amongst other products (terpinyl acetate, neryl acetate), geranyl acetate is formed.*

Since geraniol is a primary alcohol containing two ethylenic linkages, it is a highly reactive substance and its properties have been closely studied. When reduced with hydrogen in the presence of platinum black it yields a mixture of the saturated alcohol, 2:6-dimethyloctan-8-ol, and the hydrocarbon, 2:6-dimethyloctane,[†] whilst by the Sabatier-Senderens method, using a nickel catalyst, Enklaar[‡] obtained the same products and in addition a cyclic alcohol, C₁₀H₂₀O. With colloidal platinum and palladium, Paal[§] has shown that it is possible to limit the reduction to one ethylenic linkage with formation of citronellol, which according to Hesse^{||} is also formed when geraniol is boiled with sodium in the presence of hydrogen. The catalytic reduction of geraniol has been the subject of study by Grignard and Escourrou[¶]

* Bouchardat, *Compt. rend.* 1893, **116**, 1253; Tiemann and Semmler, *Ber.* 1893, **26**, 2714; Stephan, *J. pr. Chem.* 1898 [ii], **58**, 111.

[†] Willstätter and Mayer, *Ber.* 1908, **41**, 1475; Natelson, Gottfried and Kornblau, *J. Amer. C.S.* 1942, **64**, 1484.

[‡] *Ber.* 1908, **41**, 2083.

[§] *G.P.* 298193, 346949; compare also Ipatiev, *Ber.* 1912, **45**, 3222; Ishizaka, *ibid.* 1914, **47**, 2453.

^{||} *G.P.* 256716.

[¶] *Bull. Soc. chim.* 1925 [iv], **37**, 542, 546; compare also Grignard and Dœuvre, *ibid.* 1927 [iv], **41**, 999; Escourrou, *ibid.* 1928 [iv], **43**, 1091, 1211.

and they conclude that the alcohol formed is a mixture of citronellol and rhodinol, the latter alcohol, estimated by the yield of acetone obtained on ozonolysis, predominating. These experiments, although they have been adversely criticised by Verley,* and by Dupont, Desreux and Dulou† who claim that the product is free from rhodinol, support the suggestion made above that geraniol from natural sources is a mixture consisting of varying proportions of the α - and β -forms.

When geraniol is heated with concentrated alcoholic potassium hydroxide at 150° it yields *methylheptenol*.‡ The primary product of the reaction is the ketone, *methylheptenone*, which is reduced by the alcoholic potassium hydroxide. Grignard and Dœuvre§ have shown that the methylheptenol formed is a mixture of the α - and β -forms.

The action of mineral acids and dehydrating agents on geraniol is very diverse and markedly dependent on the experimental conditions employed. When the alcohol is shaken with dilute sulphuric acid (5 per cent.) the main product of the reaction is *terpin hydrate*,|| which is indirectly formed from α -terpineol, the primary product of the reaction. This cyclic alcohol is also obtained¶ when an acetic acid solution of geranyl acetate containing 1–2 per cent. of sulphuric acid is allowed to stand for 15 days. The conversion of geraniol into α -terpineol is of theoretical importance in view of its bearing on the configuration of the former alcohol. Acetic acid or acetic anhydride will not alone convert geraniol into α -terpineol, although both these reagents will convert linalool into α -terpineol or its acetate. As has already been mentioned (p. 46), the cyclisation with dilute sulphuric acid proceeds much more slowly than is the case with linalool and nerol. The most simple explanation would appear to be that, geraniol having the *cis*-configuration (XIV), the formation of the cyclic alcohol takes place in accordance with the following scheme:**

* *Bull. Soc. chim.* 1928 [iv], **43**, 854; compare Dœuvre, *ibid.* 1929 [iv], **45**, 140, 352.

† *Loc. cit.*

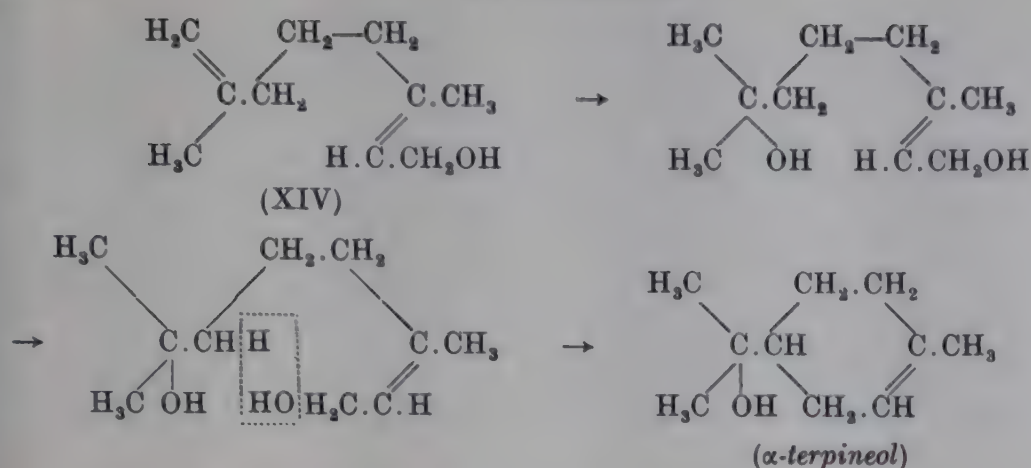
‡ Barbier, *Compt. rend.* 1898, **126**, 1423; Tiemann, *Ber.* 1898, **31**, 2991.

§ *Bull. Soc. chim.* 1927 [iv], **41**, 999.

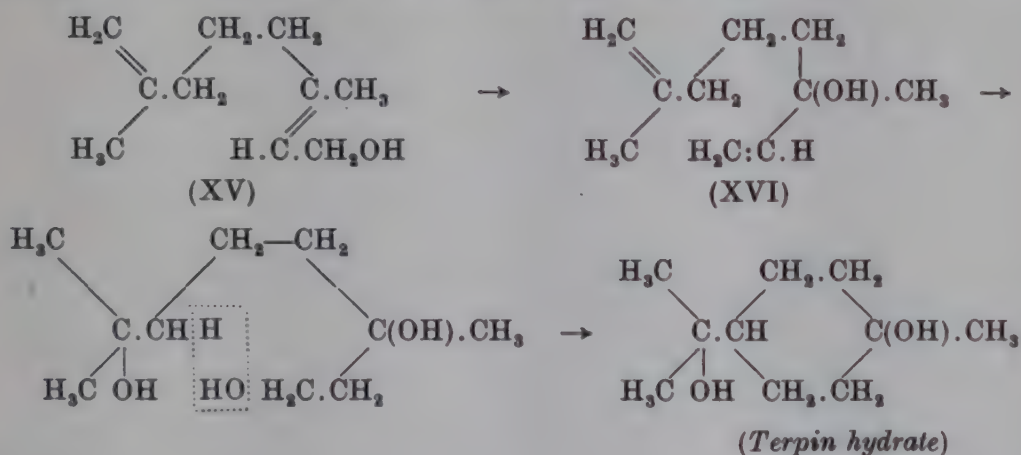
|| Tiemann and Semmler, *Ber.* 1895, **28**, 2137.

¶ Bertram and Gildemeister, *J. pr. Chem.* 1894 [ii], **49**, 194.

** Zeitschel, *Ber.* 1906, **39**, 1780.



Semmler has suggested that the conversion of geraniol into α -terpineol and terpin hydrate proceeds by the intermediate formation of linalool (XVI) in the following manner:



If this suggestion be accepted, it is somewhat difficult to account for the difference in the speed of reaction of nerol and geraniol and the former scheme would appear to be preferable.

For the conversion of geraniol into cyclic alcohols with the hydroxy group in the side chain, it is necessary to protect this group by acetylation prior to cyclisation.* The chemistry of these substances is discussed on p. 114.

Geraniol can readily be converted into *dipentene*, the formation of this cyclic terpene being brought about by treatment with phosphoric acid,[†] with active charcoal at 200°,[‡] by gaseous hydrogen chloride,[§] and other reagents, whilst, according to

* Haarmann and Reimer, *G.P.* 138141.

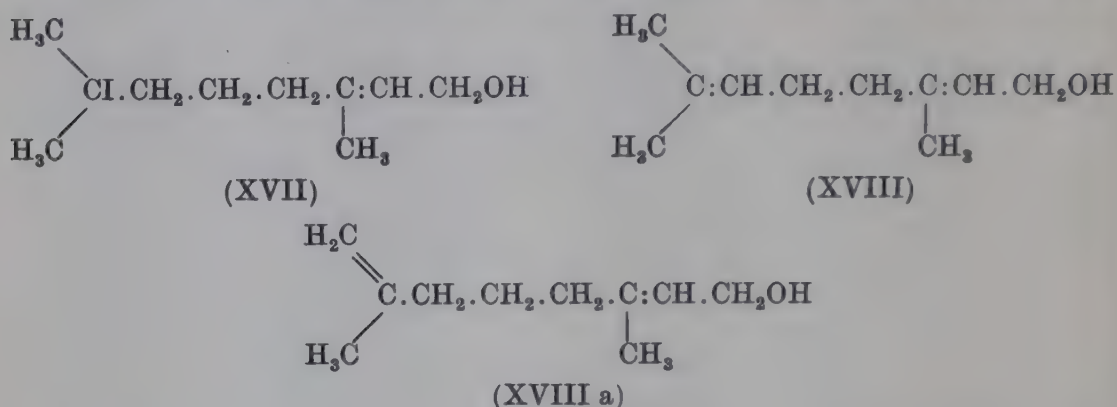
† Eckart, *Arch. Pharm.* 1891, **229**, 380; *Ber.* 1891, **24**, 4205.

‡ Kimura, *Bull. Chem. Soc. Japan*, 1935, **10**, 330.

§ Monnet and Barbier, *Compt. rend.* 1893, **117**, 1094.

Bertram and Gildemeister,* on digestion with formic acid (*d* 1.22) a mixture of terpinene and dipentene is obtained. The pyrolysis of geraniol has been investigated by Dœuvre and Desmule.†

When geraniol is treated with hydrogen iodide, it yields according to Verley‡ a *monohydroiodide* (XVII), which on treatment with alkali is converted into pure *nerol* (XVIII). This reaction cannot be regarded as direct evidence in support of the constitution of nerol, since the elimination of hydrogen iodide would probably proceed with equal facility to yield (XVIII a).



By the action of phosphorus trichloride on geraniol, Tiemann and Schmidt§ obtained *geranyl chloride*, which can also be prepared in a similar manner from linalool. This substance has been carefully investigated by Forster and Cardwell,|| Dupont and Labaune,¶ and Ruzicka.** Forster and Cardwell prepared the chloride by the action of thionyl chloride on geraniol in pyridine solution, Dupont and Labaune by treatment of either geraniol or linalool with gaseous hydrogen chloride in toluene solution, and Ruzicka by Tiemann and Schmidt's method, using light petroleum as a diluent. The chloride obtained by any of these methods is an oil, b.p. 95–96°/6 mm., which can be characterised by the preparation of a crystalline *nîtrosate*, m.p. 101°. Its constitution (XXII) was established by Forster and Cardwell, who showed that, when it was condensed with ethyl sodioacetate, an ester was obtained, which on hydrolysis gave a ketone, *geranyl acetone*, identical with dihydro-*ψ*-ionone (XXI).

* *J. pr. Chem.* 1894 [ii], **49**, 194; 1896 [ii], **53**, 236.

† *Bull. Soc. chim.* 1936 [v], **3**, 196.

‡ *Ber.* 1896, **29**, 921.

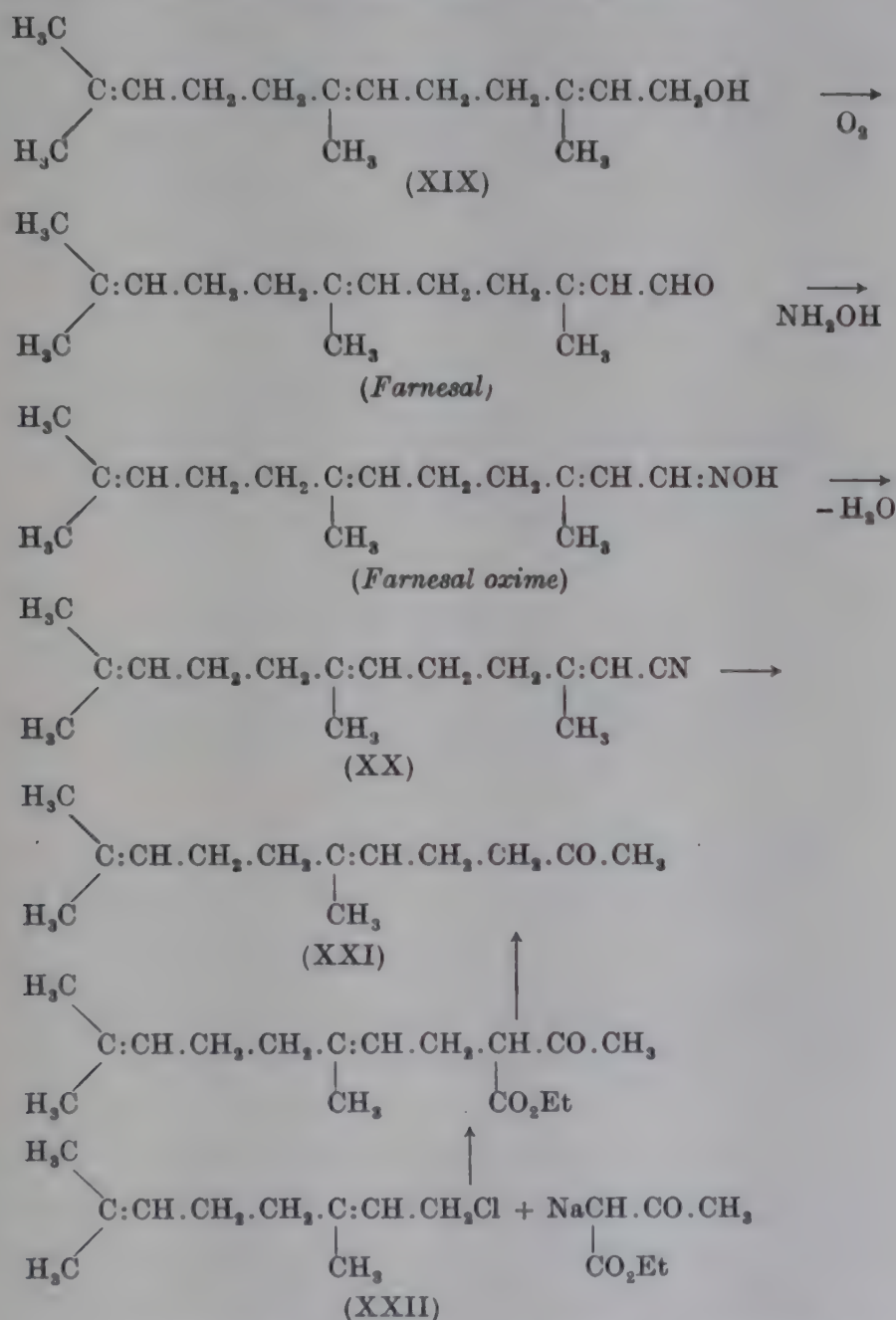
§ *Ibid.* 1919 [iv], **25**, 68.

|| *J.C.S.* 1913, **103**, 1339.

¶ *Sci. Ind. Rep. Roure-Bertrand Fils*, 1909 [ii], **10**, 19; 1911 [iii], **3**, 1.

** *Helv. Chim. Acta*, 1923, **6**, 499.

This ketone had been prepared previously by Kerschbaum* from the *nitrile* of *farnesenic acid* (XX), the constitution of which was known by its derivation from farnesol† (XIX). The reactions involved are indicated by the following scheme:



Recently, Carroll‡ has shown that geranyl acetone may also be prepared by the reaction of ethyl acetoacetate with geraniol or linalool in the presence of a trace of sodium ethoxide.

* Ber. 1913, 46, 1735.

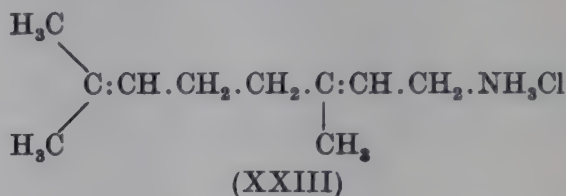
‡ J.C.S. 1940, p. 704.

† Harries and Haarmann, *ibid.* p. 1737.

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Geranyl bromide,* b.p. 102–103°/6 mm., is prepared by the treatment of either geraniol or linalool with hydrogen bromide in toluene solution.

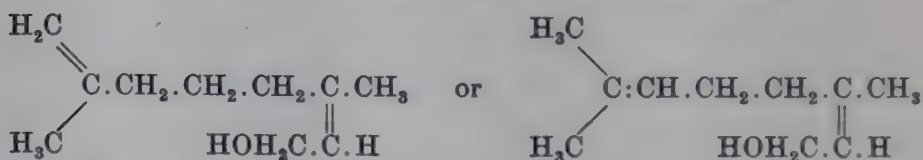
Geranylamine and its *hydrochloride*, m.p. 120°, as originally prepared from geranyl chloride by Forster and Cardwell, was probably a mixture of Δ^1 and Δ^2 isomers. Sutton† has recently obtained a hydrochloride of m.p. 145–146°, the X-ray structure of which‡ indicates that it is entirely composed of the Δ^2 -form (XXIII).



The esters of geraniol have been prepared from numerous organic acids and find application in the manufacture of artificial perfumes. The *acetate* occurs in nature in a number of essential oils.

NEROL

(trans-2:6-Dimethyl- $\Delta^{1:6}$ -octadien-8-ol or
trans-2:6-Dimethyl- $\Delta^{2:6}$ -octadien-8-ol)



Nerol, $\text{C}_{10}\text{H}_{18}\text{O}$, an alcohol which is isomeric with geraniol, occurs in nature in neroli, petit-grain, bergamot and a number of other essential oils. It was first isolated by Hesse and Zeitschel§ from neroli oil.

Soden and Treff|| found that it was most conveniently separated from the terpene alcohol fraction of essential oils, after removal as completely as possible of the geraniol present with calcium chloride, by conversion of the crude nerol, which usually still contains from 20 to 30 per cent. of geraniol, into its crystalline

* *Sci. Ind. Rep. Roure-Bertrand Fils*, 1909 [ii], 10, 19; 1911 [iii], 3, 1.

† *J.C.S.* 1944, p. 306; compare Kharasch, Nudenberg and Fields, *J. Amer. C.S.* 1944, 66, 1276.

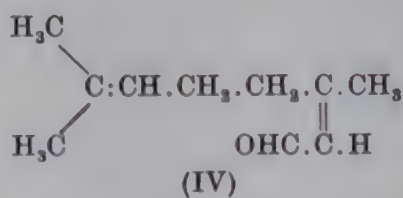
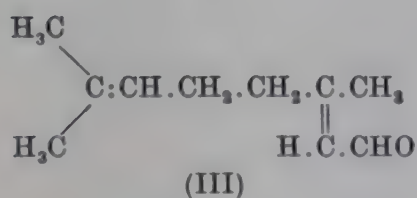
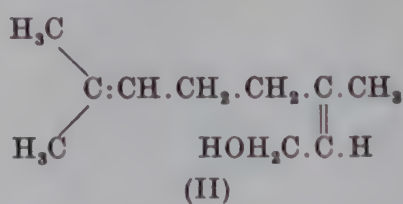
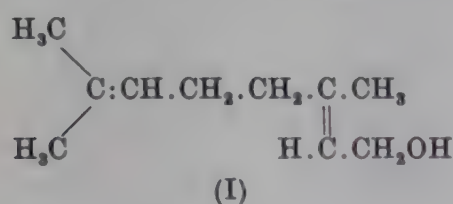
‡ Bateman and Jeffrey, *Nature*, 1943, 152, 446; Jeffrey, *Proc. Roy. Soc.* 1945, 183 A, 383.

§ *J. pr. Chem.* 1902 [ii], 66, 502.

|| *Ber.* 1904, 37, 1094; 1906, 39, 906.

diphenylurethane. The latter, after purification by crystallisation from methyl alcohol and light petroleum, melted at 52–53° and, when hydrolysed with an alcoholic potassium hydroxide solution, gave pure nerol, b.p. 225–226°, 125°/25 mm., d^{15}_D 0.8813, $\alpha_D \pm 0^\circ$. Nerol is an oil possessing a smell quite different from that of geraniol, being blander and of greater value for the manufacture of perfumes. It was found by Zeitschel* to be formed when linalool (or its esters) was treated with acid reagents. Nerol is most readily characterised by the preparation of its *tetrabromide*, m.p. 116–118°. The *allophanate* has m.p. 84°.†

V. Soden and Treff‡ found that when nerol was oxidised with chromic acid mixture it gave an aldehyde which resembled citral in its properties and yielded on condensation with cyanoacetic acid β -citrylidenecyanoacetic acid together with a little of the α -acid. It thus differs from geraniol, which on oxidation gives an aldehyde consisting mainly of citral *a*. It was further shown by Zeitschel that, on hydration with dilute sulphuric acid, nerol, like geraniol, gave α -terpineol (and terpin hydrate), but that the reaction proceeded with much greater facility. These observations led Zeitschel to suggest that geraniol and nerol are stereoisomerides and have respectively configurations (I) and (II).



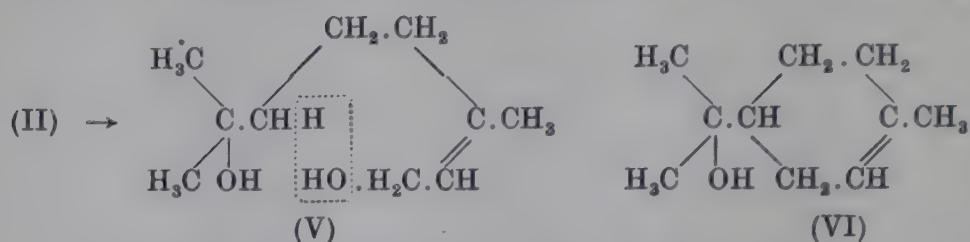
The view that citral *a* and citral *b* are stereoisomerides was generally accepted as the result of the investigations of Tiemann and his collaborators (p. 84), citral *a* would then be represented by formula (III) and citral *b* by (IV). It was further pointed out by Zeitschel, that this difference in configuration would explain

* *Ber.* 1906, **39**, 1780.

† Naves and Grampoloff, *Helv. Chim. Acta*, 1942, **25**, 1500.

‡ *Ber.* 1904, **37**, 1094; 1906, **39**, 906.

also the greater ease with which nerol is converted into α -terpineol (VI), if we assume the intermediate formation of the glycol (V).



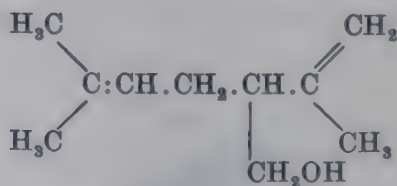
In the case of geraniol a similar reaction requires an inversion and hence the greater stability of this alcohol (compare p. 48).

This view received further support from the experiments of Blumann and Zeitschel,* who showed that very carefully purified specimens of geraniol and nerol, obtained from the oil of *Helichrysum angustifolium*, gave, on oxidation with potassium permanganate followed by chromic acid mixture, the same products, acetone and levulinic acid, in identical yields. The yield of acetone was in the one case 54 per cent. and in the other 55.5 per cent. of the theoretical quantity. This would appear to establish definitely the position of the ethylenic linkage in nerol, but, in view of the results obtained in the cases of geraniol and citral, it is very probable that nerol is a mixture of the $\Delta^{1:6}$ - and $\Delta^{2:6}$ -octadienol in which the $\Delta^{2:6}$ -isomeride predominates. It would be of great interest to examine the products formed by the action of ozone on the apparently homogeneous diphenylurethane.

In its general properties nerol resembles geraniol; the Raman spectra of the two alcohols are almost identical.† The *formyl* and *acetyl* derivatives of nerol have been described by v. Soden and Zeitschel.‡

LAVANDULOL

(2:6-Dimethyl-5-hydroxymethyl- $\Delta^{2:6}$ -heptadiene)



* Ber. 1911, 44, 2590.

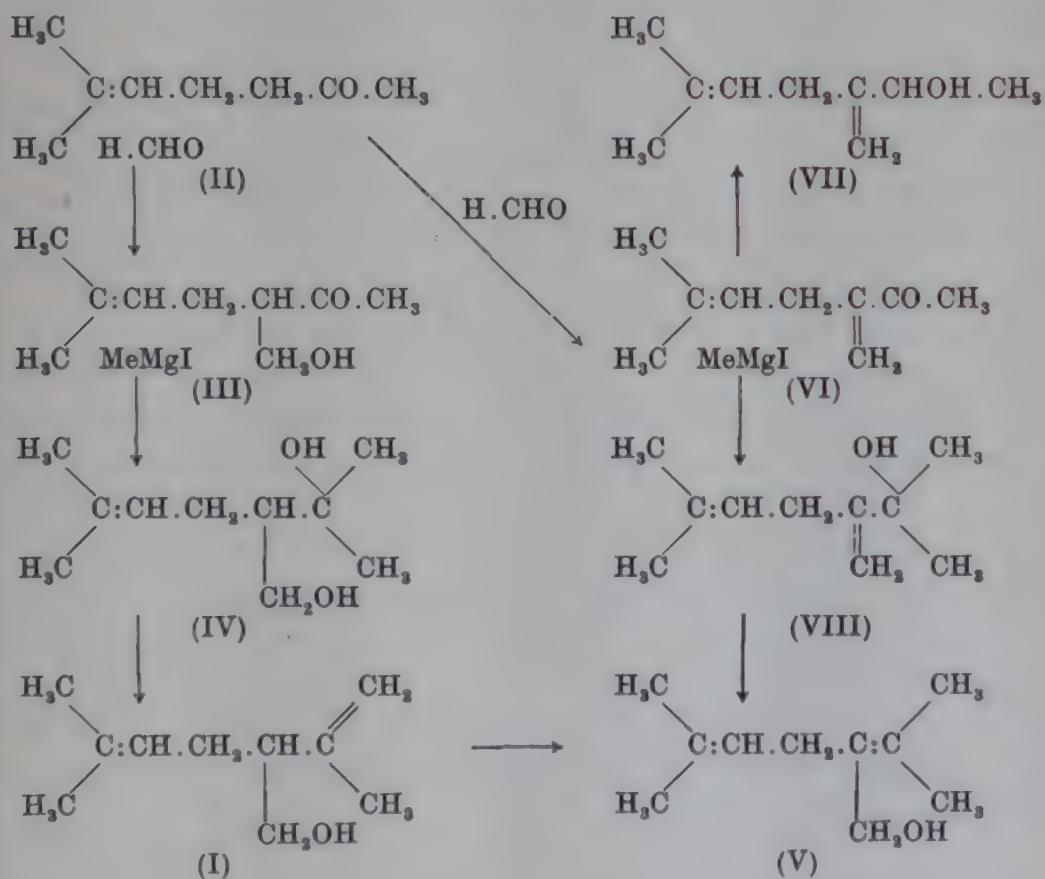
† Dupont, Desreux and Dulou, Bull. Soc. chim. 1937 [v], 4, 2016.

‡ Ber. 1903, 36, 265.

The alcohol, *lavandulol*, $C_{10}H_{18}O$, occurs in the free state and in the form of esters in French lavender oil, from which it was isolated by Schinz and Seidel* as a fragrant oil with an odour similar to that of geraniol, but unlike geraniol it does not form a compound with calcium chloride.

The presence of two ethylenic linkages is indicated by hydrogenation to *tetrahydrolavandulol*, b.p. $93-94^{\circ}/12$ mm., $\alpha_D^{20} + 12.84^{\circ}$ (*allophanate*, m.p. $101-102^{\circ}$). On oxidation with potassium permanganate or with ozone it gives formaldehyde, acetone and oxalic acid, together with a mixture of more complex products.

Schinz and Seidel observed that the properties of *lavandulol* were very similar to those of an *alcohol* (I) which had been prepared by Ruzicka and Roethlisberger† by the condensation of *methyl heptenone* (II) with formaldehyde followed by treatment of the resulting *keto-alcohol* (III) with methyl magnesium



* *Helv. Chim. Acta*, 1942, 25, 1572; see also Seidel, Schinz and Müller, *ibid.* 1944, 27, 663.

† *Ibid.* 1935, 18, 439.

iodide and dehydration of the glycol (IV).^{*} A direct comparison could not be made owing to the racemic nature of the synthetic alcohol, and it was therefore decided to isomerise lavandulol into the corresponding $\alpha\beta$ -unsaturated alcohol, which would be optically inactive. This was accomplished by Schinz and Bourquin[†] by treatment of lavandulyl acetate with hydrogen bromide, removal of hydrogen bromide from the addition product by means of pyridine, hydrolysis of the acetate and final purification through the hydrogen phthalate, when a somewhat impure *isolavandulol* (V) was obtained. From this the pure optically inactive *allophanate*, m.p. 139–140°, was prepared. *isoLavandulol* was synthesised from methyl heptenone (II), the condensation of the ketone with formaldehyde being carried out under conditions differing somewhat from those employed by Ruzicka and Roethlisberger, yielding the *methylene* derivative (VI), which was purified through its *semicarbazone*, m.p. 163–165°. It was characterised further by reduction with aluminium isopropoxide to the *alcohol* (VII) (*allophanate*, m.p. 97°). The *methylene* ketone (VI) reacted normally with methyl magnesium iodide and the tertiary alcohol (VIII) (*phenylurethane*, m.p. 81–82°) was then made to undergo an allyl isomerisation by treatment of the bromide with potassium acetate and subsequent hydrolysis to the primary alcohol (V). The *allophanate* of this, although having a slightly higher melting-point (143–144°) than that from *isolavandulol*, did not depress the melting-point of the latter. It is possible that this slight difference in the melting-points may be due to a variation in the proportions of the *isopropenyl* and *isopropylidene* forms contained by each, and there would appear to be little doubt that the synthetic alcohol is essentially identical with *isolavandulol*. Unfortunately the quantity of the latter was insufficient for the preparation of a large range of derivatives, but from the synthetic alcohol were prepared the 3:5-*dinitrobenzoate*, m.p. 74–75°, and *dl-tetrahydroisolavandulol* (*dl-tetrahydrolavandulol*), b.p. 90–100°/11 mm. (*allophanate*, m.p. 99–100°).

^{*} Ruzicka and Roethlisberger considered their product to be the $\alpha:\beta$ -unsaturated alcohol (V), but the $\beta:\gamma$ structure is more probable (compare Pfau and Plattner, *Helv. Chim. Acta*, 1932, 15, 1250), and this structure is supported by the absorption spectrum of the *allophanate* (Schinz and Bourquin, *ibid.* 1942, 25, 1598).

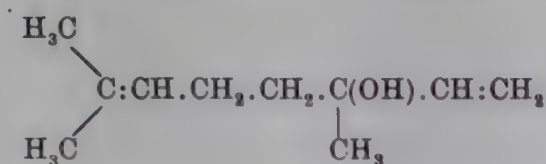
[†] *Ibid.* 1942, 25, 1591.

Lavandulol, purified through its *allophanate*, m.p. 117–118°, $[\alpha]_D^{20} - 8.5^\circ$, has b.p. 94–95°/13 mm., $d_4^{17} 0.8785$, $n_D^{17} 1.4683$, $\alpha_D^{16} - 10.20^\circ$. The *acetate* is an oil, b.p. 61–63°/0.3 mm., whilst the 3:5-*dinitrobenzoate* has m.p. 59–60° and the *anthraquinone-2-carboxylate*, m.p. 62–63°.

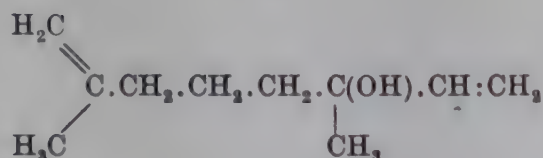
Although the structure of lavandulol cannot yet be regarded as fully established it is evident that (I) is the most probable formula. The alcohol thus offers another example of an unusual arrangement of isoprene units in a terpene molecule.

LINALOOL

(2:6-Dimethyl- $\Delta^{2:7}$ -octadien-6-ol or
2:6-Dimethyl- $\Delta^{1:7}$ -octadien-6-ol)



or



The unsaturated tertiary alcohol, *linalool*, $\text{C}_{10}\text{H}_{18}\text{O}$, which has also been known as *licareol* and *coriandrol*, would appear to have been first isolated in a pure state by Kawalier,* and was studied in greater detail by Grosser† who showed that it has the formula $\text{C}_{10}\text{H}_{18}\text{O}$, and by Morin.‡ Unlike geraniol and nerol, linalool is optically active and the laevorotatory form was separated by Morin from oil of linaloe distilled in French Guiana. The botanical origin of the tree from which this oil is obtained has been in considerable dispute, but there is now little doubt that it is obtained from the wood of *Ocotea candata* Mez, the local name for which is *Licari kanali*.

* *J. pr. Chem.* 1853 [i], 58, 226.

† *Ber.* 1881, 14, 2485.

‡ *Ann. chim.* 1882 [v], 25, 427.

In the Mexican oil of linaloe both the dextro- and laevorotatory forms of the oil are found, the *d*-form being present in the oil from the seeds and the *l*-form in the wood oil. *l*-Linalool also occurs, either in the free state or as an ester, in a number of other essential oils of which mention may be made of ylang-ylang, rose oil and bergamot oil, whilst *d*-linalool has been separated from coriander oil and orange oil.*

Since linalool does not yield any crystalline derivative from which it can be regenerated, it has only been isolated by careful fractional distillation; the physical constants attributed to the alcohol, therefore, vary over a somewhat wide range and depend upon its origin. The following may be regarded as average values:† b.p. 198–199°/760 mm., d_{15}° 0.870, n_D^{20} 1.4668, $[\alpha]_D - 20.7^{\circ}$ (from lime oil), $+ 19.18^{\circ}$ (from orange oil). *dl*-Linalool does not appear to occur in nature but it can be obtained by the isomerisation of geraniol.‡

For our knowledge of the chemistry of linalool, we are indebted mainly to the prolonged researches of Barbier, Tiemann and Semmler and their collaborators, the difficulty of the investigations being enhanced by the ease with which linalool is isomerised to geraniol. It was early recognised by Semmler§ that linalool is an acyclic alcohol, $C_{10}H_{18}O$, and in collaboration with Tiemann|| he showed that on oxidation with chromic acid mixture an aldehyde, $C_{10}H_{16}O$, is formed which is closely related to or identical with citral. These authors did not conclude that linalool was a primary alcohol, since it was already known that geraniol was the primary alcohol corresponding to citral.

Simultaneously, the chemistry of linalool was intensively studied by Barbier¶ and his collaborators. They worked with *l*-linalool obtained from oil of linaloe and called it licareol. As the result of these investigations, Barbier concluded that licareol was a primary acyclic alcohol containing two ethylenic linkages,

* Gildemeister and Hoffmann, *Die Ätherischen Öle*, 3rd ed. I, 422, may be consulted for a detailed list of the oils in which linalool occurs.

† Gildemeister, *Arch. Pharm.* 1895, **233**, 179; compare Naves, *Helv. Chim. Acta*, 1946, **29**, 555.

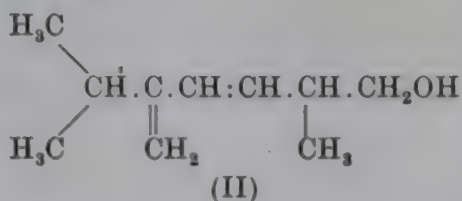
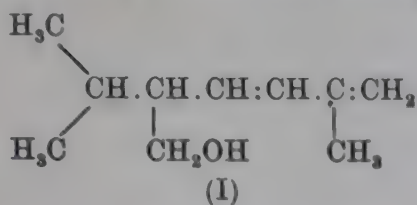
‡ *Vide infra*.

§ *Ber.* 1891, **24**, 207.

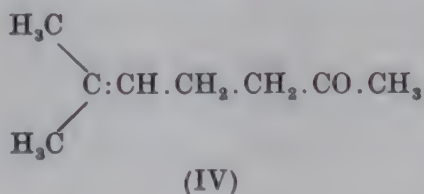
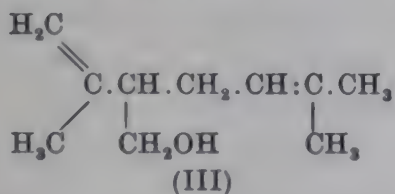
|| *Ibid.* 1892, **25**, 1184.

¶ *Compt. rend.* 1892, **114**, 674; 1893, **116**, 883, 993, 1062, 1200, 1459; *Bull. Soc. chim.* 1893 [iii], **9**, 802, 810, 914, 1002.

and he suggested that it should be represented by either formula (I) or (II), preference being given to (II).



Although Barbier was wrong in the interpretation of his results, he made a number of observations in the course of his work which were of fundamental importance in the elucidation of the constitution of linalool. He found that, when licareol (*l*-linalool) was heated with acetic anhydride, it gave a mixture of esters from which, after hydrolysis, he separated an alcohol, *licarhodol*. By oxidation of licareol with chromic acid mixture he obtained an aldehyde, *licarhodol*, $\text{C}_{10}\text{H}_{16}\text{O}$, and he regarded the alcohols, licareol and *licarhodol*, as *cis-trans*-isomerides. The reactions involved in these experiments were correctly explained by Bouchardat,* who showed *licarhodol* to be identical with geraniol and *licarhodol* with citral. Barbier had therefore observed that linalool was very readily isomerised to geraniol. In 1894 Barbier and Bouveault† showed that when linalool was oxidised with chromic acid mixture, in addition to citral, acetone and other minor products, *methylheptenone* was formed. They attempted to explain these results by formulating linalool as (III), methylheptenone being (IV), but the mechanism of the reactions involved would appear to be somewhat obscure.



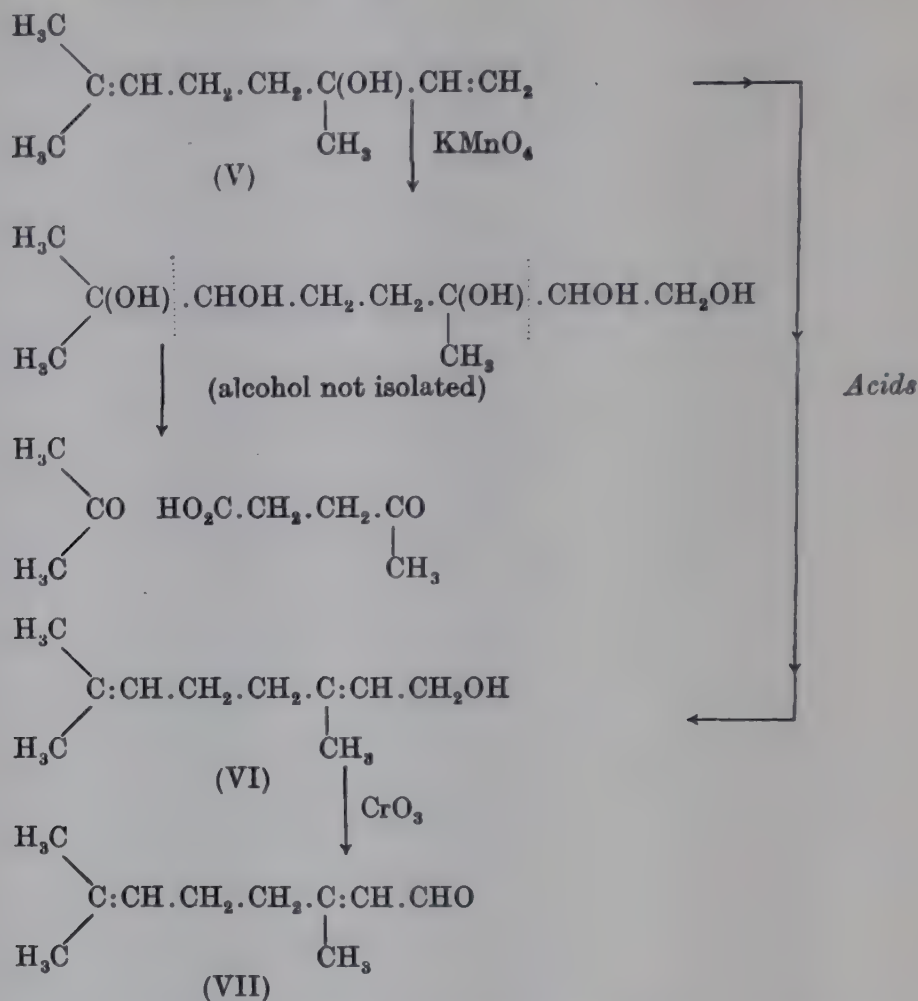
The oxidation of linalool with potassium permanganate was investigated by Tiemann and Semmler,‡ who found the products to be acetone and levulinic acid. They concluded that linalool was the tertiary alcohol represented by (V) and that the formation of citral on oxidation with chromic acid mixture was due to its ready isomerisation by acids into geraniol (VI), which then

* *Compt. rend.* 1893, 116, 1253.

† *Ibid.* 1894, 118, 1208.

‡ *Ber.* 1895, 28, 2126.

underwent oxidation to citral (VII). The reactions involved are indicated by the schematic representation shown below:

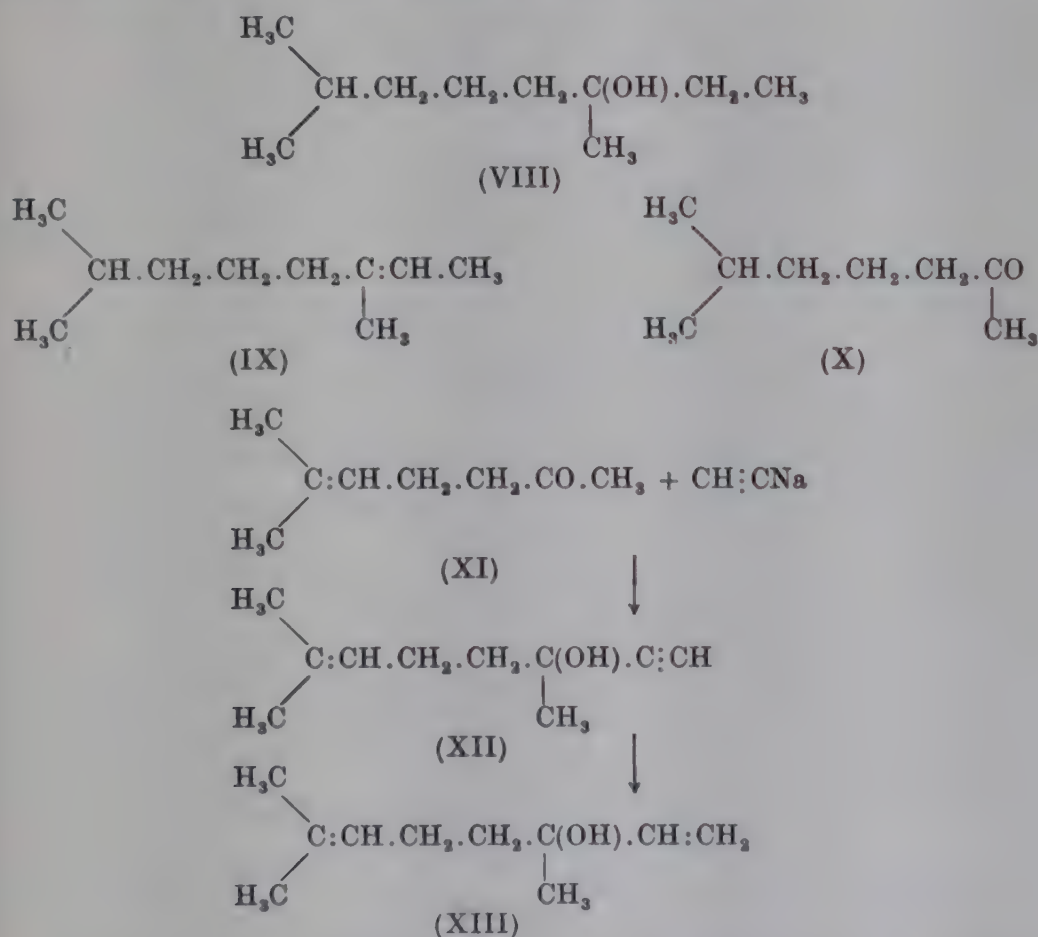


. It will be noticed that these oxidation products, acetone and levulinic acid, are identical with the products obtained under similar conditions from geraniol (p. 42), and this might be regarded as evidence in favour of Barbier's view that the two alcohols were stereoisomerides. They differ, however, in one important particular. When geraniol is treated with alkali it yields methylheptenol (see p. 42) whereas linalool is unaffected by similar treatment. Further, the low boiling-point of linalool and its physical constants are in full accord with its being a tertiary alcohol.

The formula suggested by Tiemann and Semmler met with general acceptance, although Barbier* criticised it in a number

* *Inter al.*, *Compt. rend.* 1896, **122**, 842; 1897, **124**, 1308; 1901, **132**, 1048; *Bull. Soc. chim.* 1901 [iii], **25**, 828.

of communications. In 1914, however, Barbier and Locquin* accepted the constitution and offered further valuable evidence in its support. They showed that when *l*-linalool was reduced with hydrogen in the presence of platinum black, a saturated alcohol (b.p. 86–88°/10 mm., d_4^{20} 0.851, $[\alpha]_D^{17} - 24^\circ$) (VIII) was obtained. This alcohol readily loses water, yielding an unsaturated hydrocarbon, C₁₀H₂₀, b.p. 162°, which must be represented by formula (IX) since on oxidation it gives methylisohexyl ketone (X). The constitution of the alcohol, which is also formed when linalool is hydrogenated over nickel at 130–140°,† was confirmed by its synthesis, since it is obtained when the ketone (X) is treated with ethyl magnesium iodide.



dl-Linalool was synthesised in 1919 by Ruzicka and Fornasir.‡ Utilising a reaction discovered by Nef,§ they condensed methylheptenone (XI) with sodium acetylide and obtained *dehydro*-

* *Ann. chim.* 1914 [ix], 2, 400.† Enklaar, *Rec. trav. chim.* 1908, 27, 411.‡ *Helv. Chim. Acta*, 1919, 2, 182.§ *Annalen*, 1899, 308, 264.

linalool (XII), which on reduction with sodium in moist ethereal solution gave *dl*-linalool (XIII), identical in all respects with the alcohol obtained by the isomerisation of geraniol (p. 63).

This synthesis would appear to leave no doubt that linalool should be regarded as 2:6-dimethyl- $\Delta^{2:7}$ -octadien-6-ol, a conclusion which is supported by Dupont, Desreux and Dulou,* from an examination of the Raman spectrum of the alcohol. However, attention must be directed to the suggestion of Verley,† to which reference has already been made in discussing the constitution of geraniol (p. 43). According to Verley the isomeride should be regarded as *isolinalool*, linalool being the $\Delta^{1:7}$ -isomer. By the addition of hydrogen bromide to geraniol, followed by the removal of the halogen acid from the geranyl bromide thus obtained (p. 52), it is stated that *isolinalool* and *nerol* are formed. After purification through the *hydrogen phthalate* it would appear to have a somewhat higher boiling-point (200–207°) than linalool and also to differ in its odour. Verley is of opinion that both linalool and *isolinalool* occur in nature, the former predominating in oil of linaloe.

A careful consideration of the available data would appear to indicate clearly that both natural and synthetic linalool consist of an inseparable mixture of the $\Delta^{1:7}$ - and $\Delta^{2:7}$ -isomerides and that neither alcohol has been obtained in a state of purity.

The resolution of *dl*-linalool into its enantiomorphs has been attempted by Paolini and Divizia.‡ They prepared the strychnine salt of the *dl*-hydrogen phthalate and succeeded in effecting a partial separation into the active forms, since the alcohols regenerated from the salts had respectively the values $[\alpha]_D + 1.7^\circ$ and -1.60° . It is clear that neither alcohol was obtained in a state of optical purity.

Linalool is most readily characterised by the preparation of the *phenylurethane*,§ m.p. 63–65°, or the *p*-*xenylurethane*, m.p. 85°.|| With sodium bisulphite it yields a crystalline derivative,¶ $C_{10}H_{18}O$, $2NaHSO_3$, which is very hygroscopic.

* *Bull. Soc. chim.* 1937 [v], 4, 2016.

† *Rev. des produits chim.* 1918, 21, 352; *Bull. Soc. chim.* 1919 [iv], 25, 68.

‡ *Atti R. Accad. Lincei*, 1914 [v], 23, II, 175.

§ *J. pr. Chem.* 1903 [ii], 67, 323.

|| Naves and Grampoloff, *Helv. Chim. Acta*, 1942, 25, 1500.

¶ Dupont and Labaune, *Sci. Ind. Rep. Roure-Bertrand Fils*, 1913 [iii], 7, 3.

One of the most characteristic properties of linalool is the facility with which it can be isomerised to geraniol. As has already been mentioned (p. 59) this change was first observed, although not correctly interpreted, by Barbier,* whilst investigating the action of acetic anhydride on the alcohol. The reaction has been carefully studied by a number of investigators† who have shown that the product consists of a mixture of the esters of geraniol, nerol and *d*- α -terpineol (from *l*-linalool). This isomerisation of linalool to geraniol would appear to take place most readily in the presence of acid reagents, which explains the formation of citral when linalool is oxidised with the ordinary chromic acid mixture, but it will also occur with water alone, provided the temperature is sufficiently high.‡

The reverse change, namely, the conversion of geraniol to linalool, has also been observed in a number of reactions. When geraniol is heated in an autoclave at 200° partial conversion into linalool takes place,§ whilst it is also formed when the sodium salt of *geranyl hydrogen phthalate* is distilled in steam.||

An interesting conversion of linalool into a derivative of geraniol and a reconversion of the latter into linalool have been observed by Dupont and Labaune.¶ When linalool is treated with hydrogen chloride in toluene solution at 100° *geranyl chloride* is formed, the same product being obtained by the action of phosphorus trichloride in the presence of potassium carbonate at 0°. The constitution of the chloride, geranyl chloride, has already been discussed (p. 50) and there is no doubt that it is a derivative of geraniol. When it is treated with silver oxide in benzene solution *dl*-linalool is formed, whilst by the action of potassium acetate in toluene solution linalyl acetate results. We have therefore the following series of reactions:

* *Compt. rend.* 1892, **114**, 674; 1893, **116**, 883, 993, 1062, 1200, 1459; *Bull. Soc. chim.* 1893 [iii], **9**, 802, 810, 914, 1002.

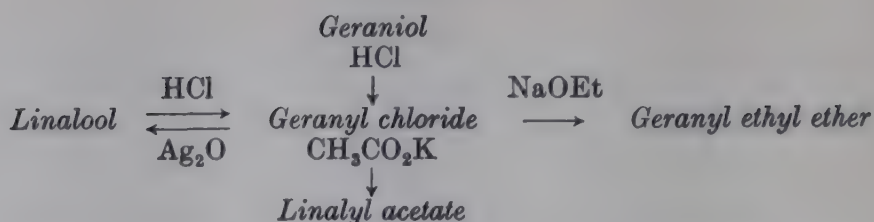
† Bouchardat, *Compt. rend.* 1893, **116**, 1253; Bertram and Gildemeister, *J. pr. Chem.* 1894 [ii], **49**, 192; Stephan, *ibid.* 1898 [ii], **58**, 109; 1901 [ii], **62**, 529; Zeitschel, *Ber.* 1906, **39**, 1780; Horiuchi, *J. Soc. Chem. Ind. Japan*, 1933, **36**, 191 B.

‡ Riwkin and Mejerson, *J. Gen. Chem. Russ.* 1935, **5**, 274.

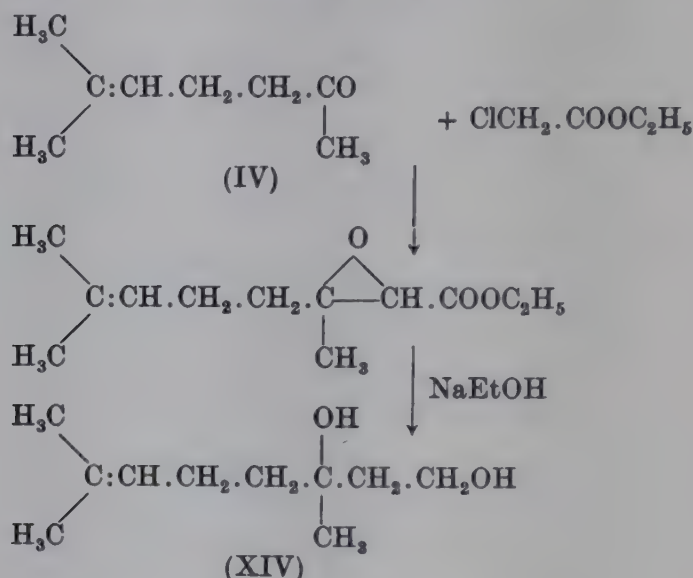
§ *Schimmel's Report*, 1898, Apr. p. 27.

|| Stephan, *J. pr. Chem.* 1899 [ii], **60**, 252.

¶ *Sci. Ind. Rep. Roure-Bertrand Fils*, 1909 [ii], **10**, 19; 1910 [iii], **1**, 42; 1911 [iii], **3**, 3; compare Forster and Cardwell, *J.C.S.* 1913, **103**, 1339.



In the presence of water, it has usually been assumed that the conversion of linalool into geraniol, and *vice-versa*, takes place through the intermediate formation of the *glycol* (XIV). Pfau and Plattner* have synthesised this glycol from methylheptenone (IV) in the following way:

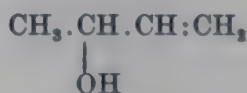


Although unsaturated alcohols were readily formed by dehydration of (XIV), the products contained no geraniol or linalool.

It is now clear that the geraniol \rightleftharpoons linalool change is an example of anionotropic rearrangement, and although the study of such transformations in the absence of conjugating influences has been mainly concerned with esters and halides,[†] the recent observations of Young, Nozaki and Warner[‡] on the interconversion of *crotyl alcohol* (XV) and *methyl vinyl carbinol* (XVI) are of considerable interest in this connection.



(XV)



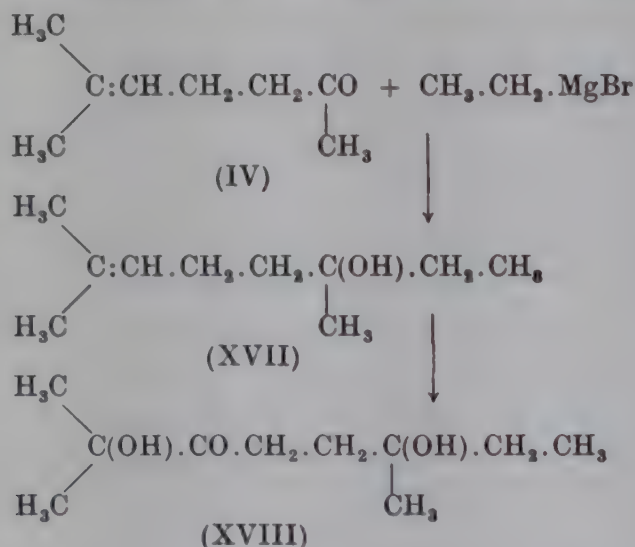
(XVI)

* *Helv. Chim. Acta*, 1932, 15, 1250.

† Watson, *Modern Theories of Organic Chemistry* (2nd ed.), 1941, p. 177.

‡ *J. Amer. C.S.* 1939, 61, 2564.

By the action of sodium on linalool both in the presence and absence of alcohol Semmler* obtained a hydrocarbon to which he gave the name *linalooleene*. This was subsequently shown to be identical with *dihydromyrcene*,† and Chablay‡ found that sodamide in the presence of liquid ammonia acted similarly. By the catalytic hydrogenation of linalool, using colloidal platinum or palladium, *dihydro-* and *tetrahydro-linalool* are formed;§ the latter alcohol, as has already been mentioned (p. 61) being also obtained if platinum black is used as the catalyst. Similar results have been obtained with Raney nickel.|| Dihydrolinalool (XVII) was synthesised by Enklaar¶ from methylheptenone (IV). Takei, Sakato and Ono** have shown that the dihydroxyketone (XVIII), m.p. 68°, is formed by permanganate oxidation of (XVII) prepared either synthetically or by reduction of linalool.



Reduction by the method of Sabatier and Senderens at 180°, using active copper as the catalyst, gives, according to Enklaar,†† a *hydrocarbon*, b.p. 68–69°/12 mm., d^{15}_D 0.834, n^{11}_D 1.48, $\alpha_D + 8.8^\circ$, which is probably cyclic and represented by either formula (XIX) or (XX).

If a lower temperature is used, 135–140°, *myrcene* results, and the same hydrocarbon is also obtained by the digestion of

* Ber. 1894, 27, 2520.

† Schimmel's Report, 1911, October, p. 128.

‡ Ann. chim. 1917 [ix], 8, 193; cf. Dupont, Dulou and Desreux, Bull. Soc. chim. 1939 [v], 6, 83.

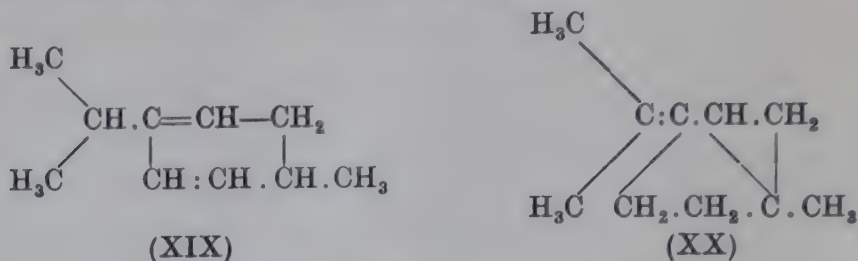
§ Paal, G.P. 298193.

|| Palfray, Bull. Soc. chim. 1940 [v], 7, 401. ¶ Rec. trav. chim. 1908, 27, 415.

** Sci. Papers Inst. Phys. Chem. Res. Tokyo, 1937, 31, 671.

†† Proc. K. Acad. Wetensch. Amsterdam, 1909, 18, 23.

linalool with phenylisocyanate.* Brooks and Humphrey† have shown that myrcene can be conveniently prepared by distilling linalool with a small quantity of iodine.



The oxidation of linalool with potassium permanganate and with chromic acid has already been discussed (p. 59). The reactions of perbenzoic acid and of permonophthalic acid on linalool have been examined by Prileschaev‡ and by Naves and Bachmann,§ the main product being *linalool monoxide*, $\text{C}_{10}\text{H}_{18}\text{O}$, b.p. $95^\circ/25$ mm., $d_4^{20^\circ}$ 0.9439, $n_D^{20^\circ}$ 1.4523, $[\alpha]_D -4.0^\circ$ (in alcohol). *Linalool dioxide*, $\text{C}_{10}\text{H}_{18}\text{O}_2$, b.p. $131\text{--}133^\circ/25$ mm., $d_{16}^{16^\circ}$ 1.0440, $n_D^{16^\circ}$ 1.4616, $[\alpha]_D +5.3^\circ$, may also be formed. Linalool monoxide, which has been shown|| to be the 2:3-epoxide, derived from the isopropylidene form of linalool, is of peculiar interest since it has been shown¶ to occur in nature, having been separated from oil of linaloe. It would appear probable that it owes its formation to the aerial oxidation of linalool whilst still in the tree.

Linalool absorbs two molecules of bromine, yielding an unstable liquid *tetrabromide*,** whilst the action of halogen acids leads to the formation of geranyl chloride and geranyl bromide (see pp. 50, 52). When shaken with dilute sulphuric acid, geraniol, nerol, *d*- (or *l*-) α -terpineol and terpin hydrate†† are formed, and the same products result from the action of formic acid when the mixture is well cooled.** At the ordinary temperature linalool reacts vigorously with formic acid, yielding dipentene and terpinene.§§

Reference has already been made to the action of acetic anhydride (p. 47) which results in the formation of geraniol,

* Enklaar, *Chem. Weekblad*, 1912, **9**, 68.

† *J. Amer. C.S.* 1918, **40**, 845.

‡ *Ber.* 1909, **42**, 4813; *J. Russ. Phys. Chem. Soc.* 1912, **44**, 613.

§ *Helv. Chim. Acta*, 1945, **28**, 1227.

|| Naves and Bachmann, *loc. cit.*

¶ *Schimmel's Report*, 1912, October, p. 80. See also Naves, *Helv. Chim. Acta*, 1945, **28**, 1231.

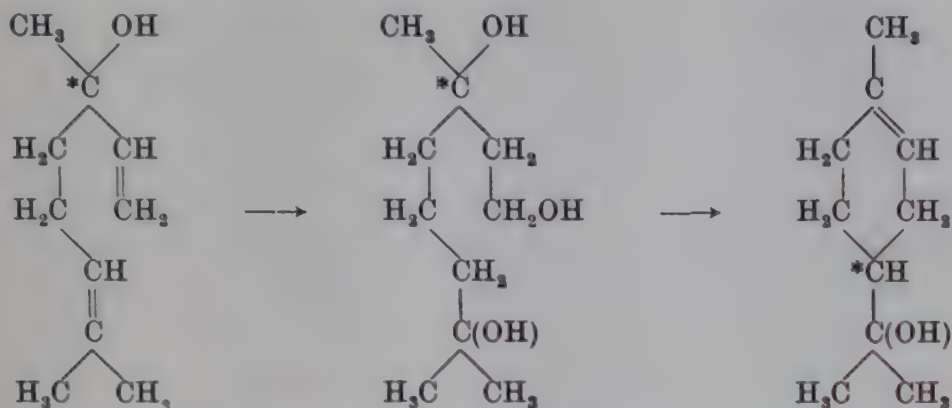
** *Bull. Soc. chim.* 1893 [iii], **9**, 1003.

†† Tiemann and Schmidt, *Ber.* 1895, **28**, 2137; Zeitschel, *ibid.* 1906, **39**, 1789.

‡‡ Stephan, *J. pr. Chem.* 1898 [ii], **58**, 116; Zeitschel, *loc. cit.*

§§ Bertram and Walbaum, *J. pr. Chem.* 1892 [ii], **45**, 601.

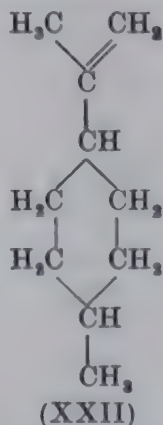
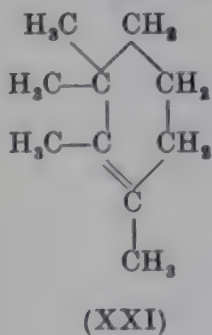
nerol, *d*- (or *l*-) α -terpineol and terpin hydrate. The mechanism of the formation of α -terpineol is probably represented by the following scheme and is of special interest, since, although an active terpeneol is formed, the original asymmetric carbon atom is destroyed, the optical activity of the α -terpineol being occasioned by another carbon atom. The carbon atoms concerned are indicated by asterisks.



It should be mentioned that the active α -terpineol is always opposite in sign to the linalool from which it is formed.

The rate of hydration of linalool to terpin hydrate is intermediate between that of geraniol and nerol, being faster than geraniol and slower than nerol.

When linalool is treated with strong sulphuric acid it is converted into a cyclic *hydrocarbon*, b.p. 165–167°, d^{17}_D 0.8112, n_D 1.4602, which, according to Semmler,[†] is possibly represented by formula (XXI) although it is not improbable that a hydrocarbon of formula (XXII) may also be present. Attention may be directed to the fact that Chapman[‡] has obtained a hydrocarbon of similar properties by the action of sodium on squalene.



[†] *Ber.* 1894, 27, 2521.

[‡] *J.C.S.* 1918, 113, 465.

Semmler and Jonas* have shown that, when the alcohol is heated with oxalic acid to a high temperature in a sealed tube, a diterpene, α -camphorene, $C_{20}H_{32}$, is formed, whilst treatment under similar conditions with the addition of isoprene leads to a sesquiterpene, *cycloisoprenemyrcene*, the constitution of which has already been discussed (p. 16). Dipentene and camphorene are the principal products obtained when the alcohol is heated with aluminium.†

Owing to the ease with which linalool is isomerised by acids the esters cannot be obtained pure by the ordinary methods. *Linalyl acetate*, which occurs very widely distributed in nature, especially in bergamot and lavender oils, was prepared by Tiemann and Semmler‡ by the interaction of the sodium derivative of linalool with acetic anhydride.

MYRCENOL

It is doubtful if the alcohol *myrcenol* has been obtained in a state of purity, and its constitution is still undetermined. It has been stated to occur in nature in the oil from the leaves of *Barosma venusta*§ and in oil of hops|| but the evidence for this would appear to be slender, since in neither case were crystalline derivatives prepared.

The alcohol was first described by Barbier,¶ who obtained it by the hydroxylation of myrcene with acetic and sulphuric acids at the ordinary temperature. The action of these reagents on myrcene had been previously investigated by Power and Kleber,** who, working at 40°, considered that linalyl acetate was formed, since the alcohol obtained on hydrolysis of the ester yielded citral on oxidation. According to Barbier, myrcenol is a colourless oil, b.p. 99–101°/10 mm., $d^{14.5^\circ}$ 0.9012, $n_D^{14.5^\circ}$ 1.4778, and it thus differs considerably in its physical constants from linalool. On treatment with acetic anhydride at 100° an *acetate*, b.p. 111–112°/10 mm., is formed.

Barbier considered myrcenol to be a tertiary alcohol and he showed that on oxidation with a mixture of potassium di-

* *Ber.* 1914, **47**, 2079.

† Winogradowa, *ibid.* 1931, **64**, 1991.

‡ *Ibid.* 1898, **31**, 839; compare Hesse and Zeitschel, *J. pr. Chem.* 1901 [ii], **64**, 256.

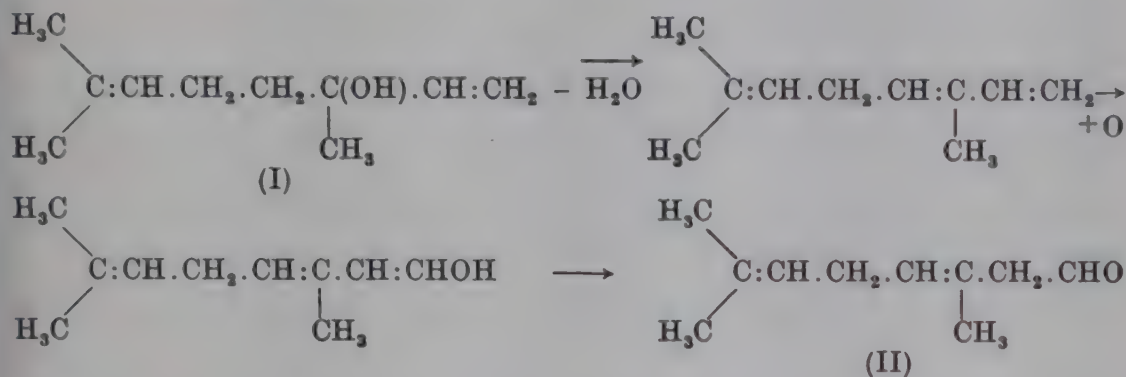
§ Jensen, *Pharm. J.* 1913 [iv], **36**, 60.

|| Rabak, *J. Agric. Res.* 1914, **2**, 115.

¶ *Bull. Soc. chim.* 1901 [iii], **25**, 688.

** *Pharm. Rundschau*, 1895, **13**, 60.

chromate and sulphuric acid it gave (1) *acetone*, (2) *levulinic acid*, and (3) an *aldehyde*, $C_{10}H_{16}O$. The aldehyde had a completely different smell from citral, and after purification through its *oxime* (b.p. $148-150^{\circ}/10$ mm.) it had b.p. $110^{\circ}/10$ mm. and gave a *semicarbazone*, m.p. $195-196^{\circ}$. Barbier concluded that myrcenol had formula (I) and explained the formation of the aldehyde (II) by the somewhat unusual series of reactions represented by the following scheme:



The formula (I) suggested by Barbier for myrcenol is identical with that now recognised as correctly representing the constitution of linalool (p. 59), whilst the aldehyde (II) considered to be formed from it on oxidation is a structural isomeride of citral (p. 83). It is clear therefore that Barbier's theoretical deductions, at any rate, must be regarded as incorrect.

In the same year (1901) Semmler* reinvestigated the properties of myrcenol and came to the conclusion that the alcohol was a mixture of linalool and α -terpineol. Later Enklaar† prepared myrcenol by Barbier's method and the constants of the alcohol obtained by him (b.p. $99^{\circ}/10$ mm., $d_{15}^{\circ} 0.9042$, $n_D^{15} 1.4806$) agreed well with those found by Barbier. Enklaar was successful in definitely establishing the existence of myrcenol by the preparation of a crystalline *phenylurethane*, m.p. 68° , which depresses the melting-points of the corresponding derivatives prepared from linalool and ocimenol. Unfortunately no evidence is as yet available as to its constitution. Semmler and Mayer‡ have shown that it cannot be reduced by sodium and alcohol and legitimately deduce from this fact that it cannot contain conjugated ethylenic

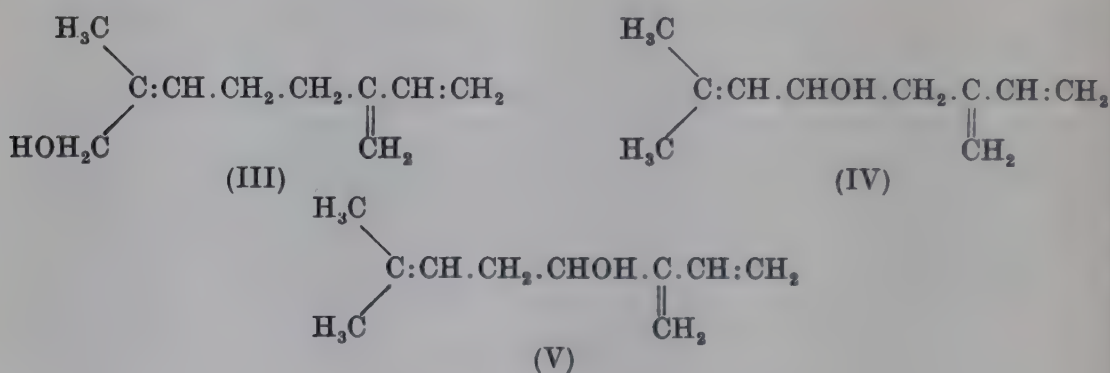
* Ber. 1901, **34**, 3128.

† Rec. trav. chim. 1907, **26**, 167.

‡ Ber. 1911, **44**, 2011.

linkages. An unsuccessful attempt was made by Paolini and Divizia* to purify the alcohol through the strychnine salt of the *hydrogen phthalate*. The salt was, however, found to be an oil which could not be obtained crystalline and which dissolved very readily in all solvents. They conclude that myrcenol, as prepared by Barbier's method, is a mixture of alcohols and this would appear to be probable, but further work, having as its aim the purification of the alcohol and the determination of its constitution, is desirable.

Mention has already been made (p. 19) of a "*myrcenol*" obtained by the action of selenium dioxide on myrcene. It is doubtful if this alcohol, which yields an *allophanate*, m.p. 110–111°, is homogeneous. It would seem probable that it is a mixture of the primary and secondary alcohols represented by (III), (IV) and (V).



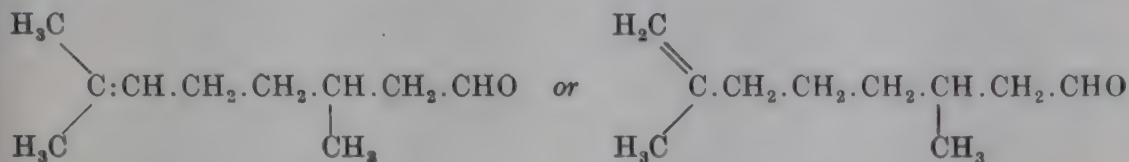
* *Atti R. Accad. Lincei*, 1914 [v], 23, II, 176.

CHAPTER III

ALDEHYDES

CITRONELLAL (RHODINAL)

(2:6-Dimethyl- Δ^2 -octen-8-al or 2:6-Dimethyl- Δ^1 -octen-8-al)



Citronellal was first separated by Gladstone* from citronella oil, which is derived from the grass *Cymbopogon Nardus* L., and was later examined by Wright.† The formula $\text{C}_{10}\text{H}_{16}\text{O}$ or $\text{C}_{10}\text{H}_{18}\text{O}$ was assigned to it, neither of these authors however determining whether it was an alcohol, aldehyde or ketone. Kremers‡ first recognised that it was an aldehyde. He separated it from citronella oil by utilising the compound which it gives with sodium bisulphite but he erroneously regarded it as heptaldehyde, $\text{C}_7\text{H}_{14}\text{O}$. Dodge§ in 1889 separated the aldehyde from the same oil and correctly assigned to it the formula $\text{C}_{10}\text{H}_{18}\text{O}$.

Citronellal does not apparently occur very widely distributed in nature. The dextrorotatory form is found in Ceylonese citronella oil (from *C. Nardus*) and in the oils from *Eucalyptus maculata* var. *citriodora* and *E. dealbata*; the laevorotatory form has been found in Javanese citronella oil and in the oil from *Pinus Jeffereyi*.||

The first detailed experiments on the constitution of citronellal were made by Semmler,¶ who separated the aldehyde from the oil of *Melissa officinalis*. He showed that the aldehyde, which was purified through its bisulphite compound, gave on oxidation *citronellic acid*, $\text{C}_{10}\text{H}_{18}\text{O}_2$, and he suggested that it was an olefinic aldehyde. Later** he prepared the *oxime* and converted this through the *nitrile* into the same acid. In the meantime it had

* *J.C.S.* 1872, 25, 7.

‡ *Proc. Am. Pharm. Assoc.* 1887, 35, 571.

|| Schorger, *Ind. Eng. Chem.* 1913, 5, 972.

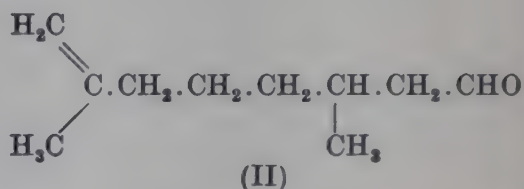
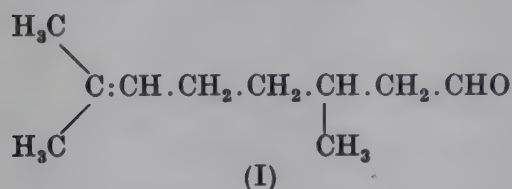
** *Ibid.* 1893, 26, 2254.

† *Pharm. J.* 1874 [iii], 5, 233.

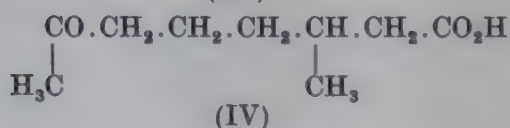
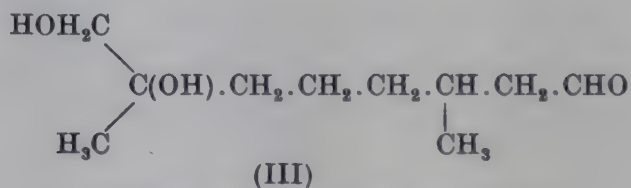
§ *Amer. Chem. J.* 1889, 11, 456.

¶ *Ber.* 1891, 24, 209.

been recognised by Dodge* and Kremers† that the aldehydes previously described by them were identical with Semmler's citronellal. In his early experiments Dodge had observed that the aldehyde could be reduced by sodium amalgam to a primary alcohol, *citronellol*, and this was subsequently confirmed by Tiemann and Schmidt.‡ The constitution of citronellol and its relationship to rhodinol has already been discussed on p. 28, and since citronellal (or rhodinal) is the corresponding aldehyde, it must be regarded as a mixture of the aldehydes represented by formulae (I) and (II).§



This conclusion, that the aldehyde is a mixture, is supported by the experiments of Harries^{||} and his collaborators, who repeated and extended the work of Harries and Schauwecker[¶] and Harries and Himmelmann.** Harries and Schauwecker had shown that, when the *dimethylacetal* of citronellal was carefully oxidised with potassium permanganate and the hydroxy-acetal so obtained hydrolysed with acid, *dihydroxycitronellal* (III) resulted, which, on further oxidation with chromic acid, gave the ketonic acid (IV).



These experiments supported the assignment of formula (II) to the aldehyde, but the experiments of Harries and Himmel-

* *Amer. Chem. J.* 1890, **12**, 553.

† *Ibid.* 1892, **14**, 203.

‡ *Ber.* 1896, **29**, 905.

§ Barbier and Bouveault originally considered that rhodinal was represented by formula (I) and citronellal by (II).

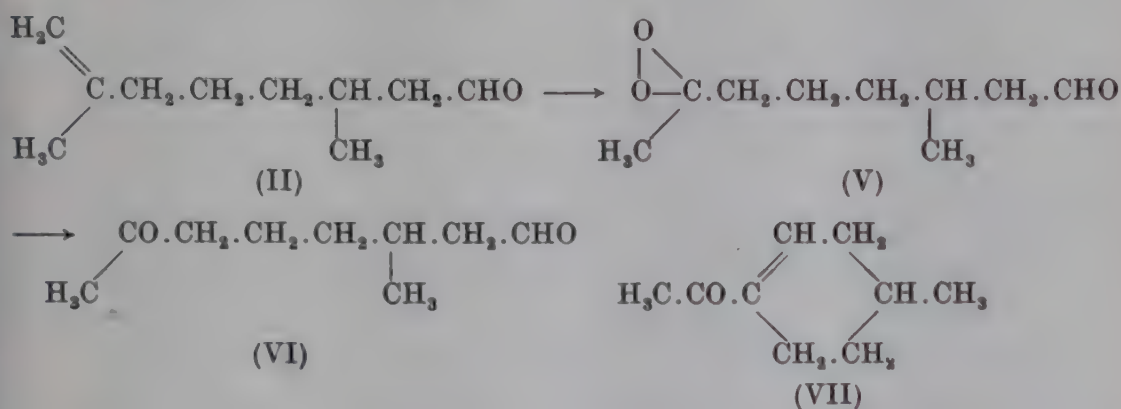
|| *Annalen*, 1915, **410**, 8.

¶ *Ber.* 1901, **34**, 2981.

** *Ibid.* 1908, **41**, 2187.

mann indicated that it was a mixture, since, on oxidation of the aldehyde with ozone, both acetone and β -methyladipic acid were formed. They considered that the mixture contained about 40 per cent. of an aldehyde of formula (I).

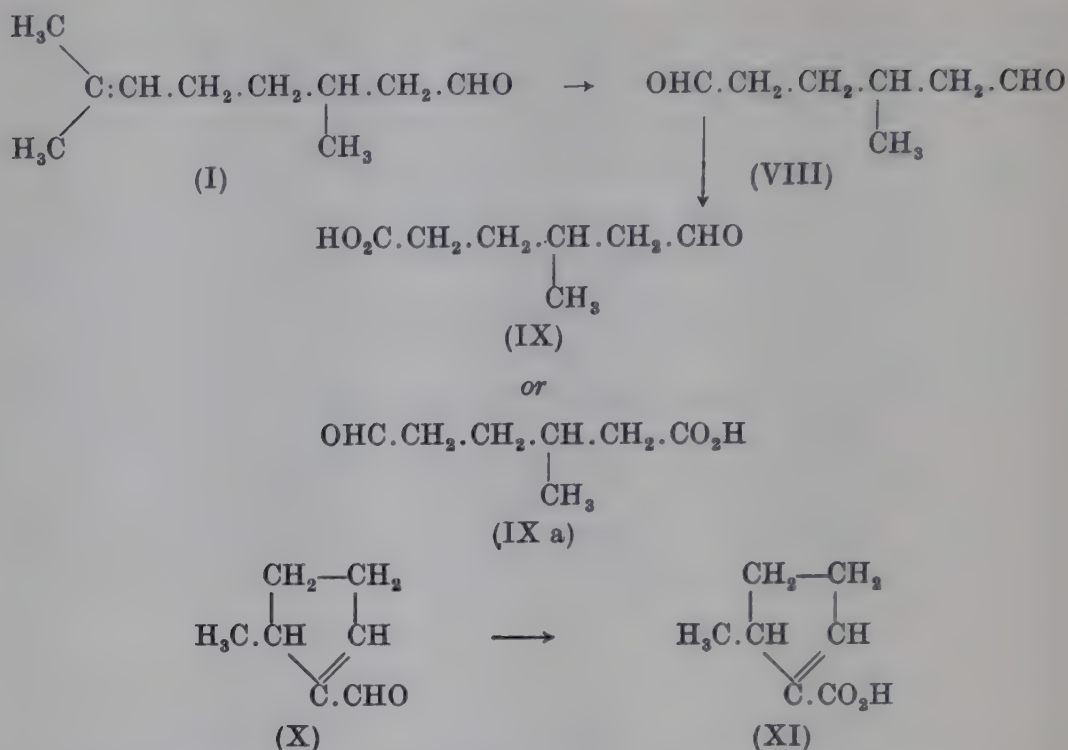
The subsequent elaborate investigations of the products of the ozonolysis of citronellal derivatives carried out by Harries in collaboration with Wagner and Comberg completely confirmed the view that citronellal was a mixture. From citronellal dimethylacetal they obtained (i) formic acid, (ii) acetone (acetone peroxide), (iii) the peroxide of *methyloctanonal* (V), (iv) the cyclic ketone (VII), (v) the *semi-aldehyde* of β -methyladipic acid (IX or IX a), (vi) *methyl- Δ^1 -cyclopenten-1-al* (X), and (vii) *5-methyl- Δ^1 -cyclopentane-1-carboxylic acid* (XI).



The separation of the peroxide (V) established the presence of the aldehyde of formula (II) in the mixture. When this was decomposed by alkali the primary product (VI) could not be isolated since it passed immediately into the cyclic ketone (VII), a substance which had been described previously by Wallach and Evans.*

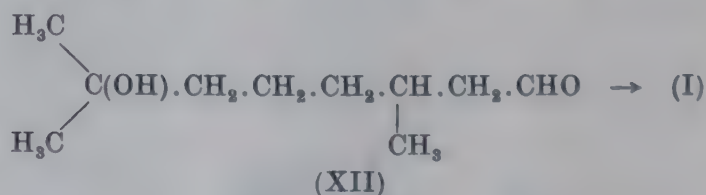
The other oxidation products were derived from the aldehyde of formula (I). The *cyclopentene* aldehyde (X) and acid (XI) are formed by the internal condensation of the primary oxidation product (VIII), the aldehyde (X) being oxidised to the acid (XI) whilst the dialdehyde (VIII) also leads to the *semi-aldehyde* of β -methyladipic acid (IX or IX a). The yields of the various oxidation products showed the aldehyde to consist approximately of 60 per cent. of (I) and 40 per cent. of (II).

* *Annalen*, 1908, **360**, 34; compare Dœuvre, *Bull. Soc. chim.* 1929 [iv], **45**, 1098.



Although these experiments showed citronellal to be a mixture, according to Tiemann and Schmidt* it gave an apparently homogeneous *semicarbazone*, m.p. 82.5° . Oxidation of this with ozone showed however that, like the parent aldehyde, it was a mixture. The conclusion reached by Harries has been fully confirmed by Rupe,[†] and, from the Raman spectrum, by Dupont, Desreux and Dulou.[‡]

Whilst this evidence would appear to be conclusive, Verley[§] considers the aldehyde separated from Javanese citronella oil to be a homogeneous substance represented by the formula (II). Following Barbier and Bouveault he retains the name, citronellal, for this aldehyde for which he found the constants: b.p. $82^\circ/2$ mm., $d_{20}^{20^\circ}$ 0.8682, $n_D^{20^\circ}$ 1.5434, $[\alpha]_D^{20^\circ}$ $+9.19^\circ$, the semicarbazone having m.p. 82.5° . Verley prepared rhodinal (I) by the



* *Ber.* 1897, 30, 34.

† *Annalen*, 1914, 402, 149; 1915, 409, 339, 353.

‡ *Bull. Soc. chim.* 1937 [v], 4, 2016.

§ *Ibid.* 1928 [iv], 43, 846; compare however Waterman and Elsbach, *ibid.* 1929 [iv], 45, 137.

dehydration of the *hydroxyaldehyde* (XII) by distillation with kieselguhr. The constants of rhodinal differ somewhat from those of citronellal: b.p. $83^{\circ}/2$ mm., d_{20}^{20} 0.8709, $[\alpha]_D^{20} +1.10^{\circ}$. The *semicarbazone* had m.p. 75.5° and when mixed with that of citronellal a depression (m.p. $73-74^{\circ}$) was observed. This depression in the melting-point cannot, however, be regarded as conclusive evidence that the two semicarbazones are structural isomerides, since the aldehydes from which they were derived were not optically pure, and in any case they must each be mixtures of the *d*- and *dl*-forms. In this connection, attention may also be directed to an investigation by Prins,* who attempted to separate citronellal and rhodinal by fractional distillation. He obtained two fractions: (a) b.p. $203-204^{\circ}$, d^{14} 0.880, n_D^{14} 1.4641, and (b) b.p. $198-200^{\circ}$, d^{14} 0.8745, n_D^{14} 1.4548. From fraction (a) a semicarbazone, m.p. $85-86^{\circ}$, was obtained, whilst that from (b) had m.p. $82.5-83^{\circ}$. As Prins himself remarks, the formation of semicarbazones of different melting-points was to be anticipated, since both fractions (a) and (b) were mixtures of the active and racemic forms and the difference in their properties could not be regarded as evidence that any separation of the isomeric aldehydes had occurred.

At present, therefore, citronellal must be regarded as being an inseparable mixture of the aldehydes represented by formulae (I) and (II), in which either the one or the other form may predominate.

Since citronellol can be oxidised to citronellal, the synthetical methods for the preparation of the alcohol given on p. 31 may be used for the aldehyde. The optimum conditions for the oxidation of the alcohol have been worked out by Tiemann and Schmidt,† but, owing to the side reactions which occur, the yield is poor. Citronellal has also been obtained by the catalytic hydrogenation of citral.*

Citronellal may be purified most conveniently through its crystalline *bisulphite* compound (see below), but great care is necessary in decomposing this with alkali owing to the instability of the aldehyde. The following constants have been

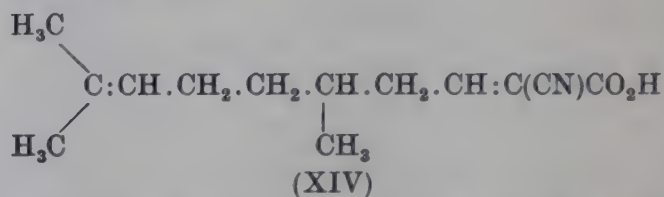
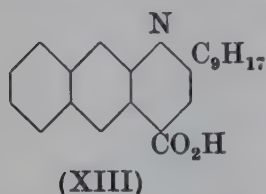
* *Chem. Weekblad*, 1916, **14**, 692; compare Grignard and Dœuvre, *Bull. Soc. chim.* 1929 [iv], **45**, 809.

† *Ber.* 1897, **30**, 33.

* Skita, *ibid.* 1909, **42**, 1634.

observed for the aldehyde purified in this manner: b.p. 205–206°, d^{20}_D 0.855, n^{20}_D 1.448, $[\alpha]_D +12.30^\circ$.

Containing as it does both an ethylenic linkage and an aldehydic group, citronellal is a highly reactive substance. It is readily characterised by the preparation of the *semicarbazone* to which reference has already been made. It may also be identified by the preparation of *citronellyl-β-naphthocinchonic acid* (XIII), m.p. 225°, which is obtained by the condensation of the aldehyde with β-naphthylamine and pyruvic acid.* Another derivative which may be used for identification is the condensation product formed with cyanoacetic acid (XIV).†



With hydroxylamine, citronellal yields a liquid *oxime*,‡ b.p. 135–136°/14 mm.; the *hydrazone* also is an oil, b.p. 135°/15 mm., and is obtained by treatment of the aldehyde with hydrazine hydrate, the *azine*, b.p. 209–213°/25 mm., being also formed.§ By treatment of the hydrazone with sodium ethoxide, an unsaturated hydrocarbon, 2:6-dimethyloctene, results, but the position of the ethylenic linkage does not appear to have been determined. The 2:4-dinitrophenylhydrazone, m.p. 78°, has been described by Allen.||

By the action of methyl alcohol containing a little hydrogen chloride (1 per cent.) citronellal is converted into the *dimethylacetal*, $C_{10}H_{18}(OCH_3)_2$, a derivative which was used by Harries and his collaborators in their investigations on the constitution of the aldehyde (see p. 72). The *diethylacetal* was prepared in a similar manner.

Citronellidene-acetic acid, formed by the condensation of citronellal with malonic acid,¶ may be reduced in the form of its phenylimidochloride, by chromous chloride, to *citronellideneacetaldehyde* (XV), b.p. 108–110°/12 mm.**

* Doebner, *Ber.* 1894, **27**, 2024.

† Tiemann, *ibid.* 1899, **32**, 824.

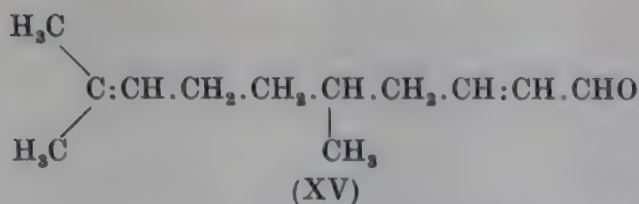
‡ Semmler, *ibid.* 1893, **26**, 2255.

§ Wolff, *Annalen*, 1912, **394**, 103.

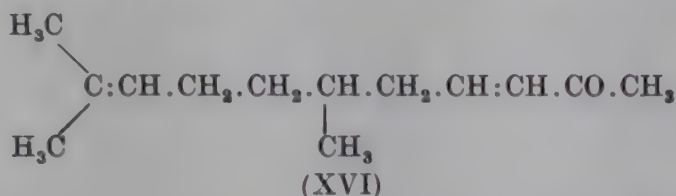
|| *J. Amer. C.S.* 1930, **52**, 2955.

¶ Rupe *et al.*, *Ber.* 1903, **36**, 2798; *ibid.* 1907, **40**, 2813; Ruzicka and Steiger, *Helv. Chim. Acta*, 1927, **10**, 684.

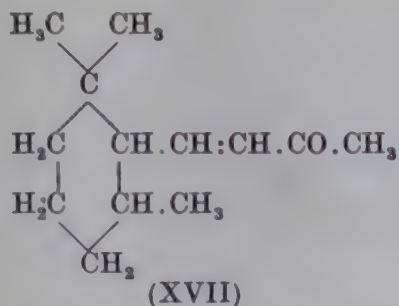
** von Braun and Rudolph, *Ber.* 1934, **67**, 1735.



Of interest also is the condensation product of citronellal and acetone first prepared by Haarman and Reimer* and subsequently investigated by Rupe and his collaborators.† This derivative, which is an oil (b.p. 153–156°/21 mm.) and is represented by formula (XVI), is formed when a mixture of acetone



and citronellal is treated with dilute alkali. This substance, which is known as *dihydropseudoionone*, like *pseudoionone* (see p. 122), is readily converted into the cyclic body *dihydroionone* (XVII), an oil b.p. 136°/23.5 mm., which has a fresh smell of flowers.



These and similar derivatives of citronellal have been studied in considerable detail by Rupe,‡ more especially with regard to the relationship of constitution to rotatory power, and he has examined also the action of the Grignard reagent on the aldehyde. In the latter connection, however, his conclusion that reaction occurs, not only with the aldehyde group in the normal manner, but also with the ethylenic linkage, has been disproved by more recent work§ which has shown that the double bond is unaffected by the Grignard reagent.

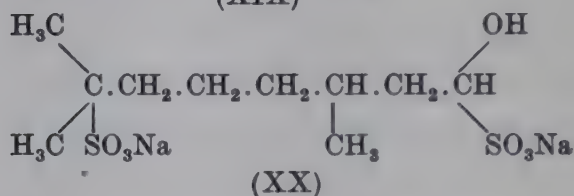
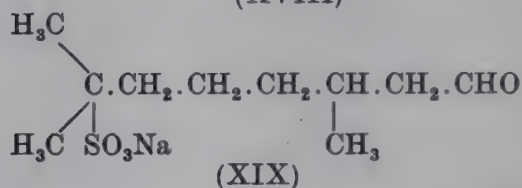
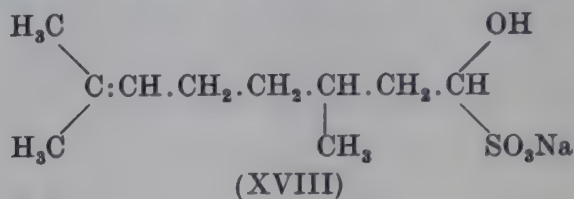
* G.P. 75128.

† Ber. 1900, 33, 857.

‡ Annalen, 1914, 402, 149; 1915, 409, 339, 353.

§ Gilman and Schulz, J. Amer. C.S. 1930, 52, 3588; Young and Siegel, *ibid.* 1944, 66, 354.

Although, as has already been mentioned, the derivative formed by the action of sodium bisulphite on citronellal may be conveniently used for the purification of the aldehyde, the reaction proceeds in a somewhat complicated manner. Since citronellal contains both an aldehydic group and an ethylenic linkage, three different compounds, represented by formulae (XVIII), (XIX) and (XX), are possible and have been prepared.



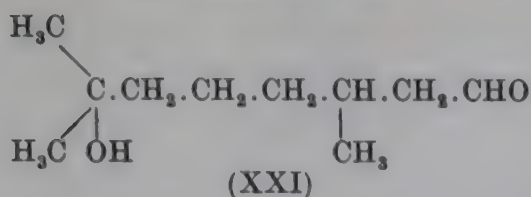
We owe our knowledge of these derivatives mainly to Tie-mann,* who has studied with great care the conditions for their formation and has developed methods for the separation of citronellal, methylheptenone and citral.† The normal bisulphite compound (XVIII) is formed when the aldehyde is shaken with an ice-cold aqueous solution of sodium bisulphite (35 per cent.) from which the excess of sulphur dioxide has been removed by a current of air. This bisulphite compound, which is crystalline, is soluble in warm water, but in boiling water it is partially decomposed with liberation of the aldehyde. The decomposition is readily effected by treatment with dilute acids or alkalis. According to Cholmer,‡ it may be hydrated with mineral acid and subsequently decomposed with alkali to yield 2-hydroxy-dihydrocitronellal (XXI). The latter, on hydrogenation, gives 2-hydroxydihydrocitronellol.§

* *Ber.* 1898, **31**, 3306; 1899, **32**, 812.

† Compare Flatau and Labbé, *Bull. Soc. chim.* 1898 [iii], **19**, 1012; Labbé, *ibid.* 1899 [iii], **21**, 77, 1026.

‡ *Chem. Zentr.* 1936, **I**, 2072; compare Verley, *Bull. Soc. chim.* 1928 [iv], **43**, 849.

§ Palfray, Sabetay and Rangel, *Compt. rend.* 1941, **212**, 911.



The bisulphite compound (XX) is obtained by treatment of the aldehyde with an excess of sodium bisulphite solution containing a little sodium sulphite. The salt can be separated in a crystalline state but it is excessively hygroscopic. When this derivative is mixed with dilute alkali it is decomposed, being converted into the mono-derivative (XIX) from which the citronellal cannot be recovered.

The corresponding *lithium* bisulphite compounds have been studied by Dodge.*

On treatment with alkaline reducing agents, owing to the presence of the aldehydic group, citronellal tends to resinify; as was however first shown by Dodge[†] and later confirmed by Tiemann and Schmidt,^{*} it can be reduced in alcoholic solution with sodium amalgam to the alcohol, *citronellol*, provided that the solution is kept faintly acid with acetic acid. By catalytic hydrogenation in the presence of either platinum or palladium, Paal[‡] succeeded in reducing the ethylenic linkage with formation of the saturated aldehyde, *dihydrocitronellal*, whilst reduction of *d*-citronellal in the presence of nickel under a moderate pressure yields the corresponding saturated alcohol, *d*-3:7-dimethyloctanol.^{||} According to Delépine and Hanegraaf,[¶] with Raney nickel the aldehyde group is reduced more rapidly than the ethylenic linkage.

With the halogens and halogen acids citronellal forms additive compounds, but these are oils which are unstable and rapidly decompose.**

The oxidation of citronellal in the presence of sunlight has been investigated by Sernagiotto^{††} and leads to a complex

* *Amer. Perf. essent. Oil Review*, 1936, 32, 67.

† *Amer. Chem. J.* 1889, 11, 456.

‡ *Ber.* 1896, 29, 905.

* G.P. 298193; see also Suzuki, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1929, 8, 573.

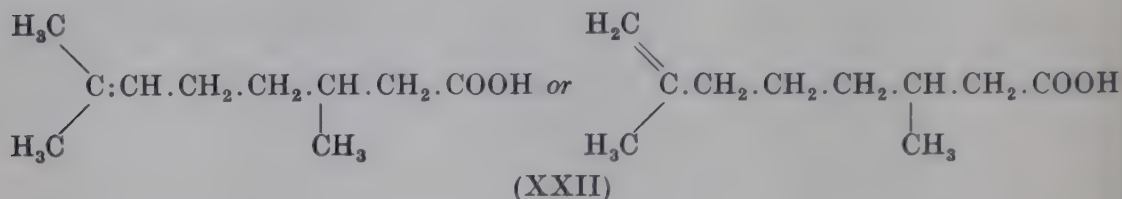
|| v. Braun and Kaiser, *Ber.* 1923, 56, 2271.

⁹ *Bull. Soc. chim.* 1937 [v], 4, 2087.

** *Amer. Chem. J.* 1892, 14, 203.

†† *Atti R. Accad. Lincei*, 1915 [v], **24**, 850; compare Waterman and Elsbach, *Rec. trav. chim.* 1934, **53**, 730.

mixture, the following being the more important substances formed: acetone, β -methyladipic acid, β -methylhexoic acid ($\text{CH}_3 \cdot [\text{CH}_2]_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$), dihydroxycitronellic acid, isopulegol and menthone. As has already been mentioned* (p. 71), gentle oxidation with silver oxide yields citronellic acid (XXII), the occurrence of which in nature has often been reported.†



With perbenzoic acid, citronellal has been shown by Prileschaev‡ to yield a *monoxide*, an oil, b.p. 130–131°/25 mm., which gives on hydration a glycol, b.p. 180–182°/18 mm. It is unlikely that either of these substances was homogeneous.

The products formed by the oxidation of citronellal with other reagents have been referred to already.

The tendency for citronellal to undergo cyclisation is very great. The action of acetic anhydride on the aldehyde was first examined by Tiemann and Schmidt,§ who showed that *isopulegol acetate* (XXV) was formed which, on hydrolysis, yielded *isopulegol* (XXVI). The mechanism of the reaction was established by the subsequent investigation of Semmler.|| He showed that the first product of the reaction was the *acetate* of the enolic form of citronellal (XXIII), together with a small quantity of the *diacetate* (XXIV).

For simplicity the reaction has been shown for the aldehyde as represented by formula (II), but it can obviously take place equally well from (I) if we assume that a shift of the ethylenic linkage occurs during the reaction, as has been observed in similar cases.

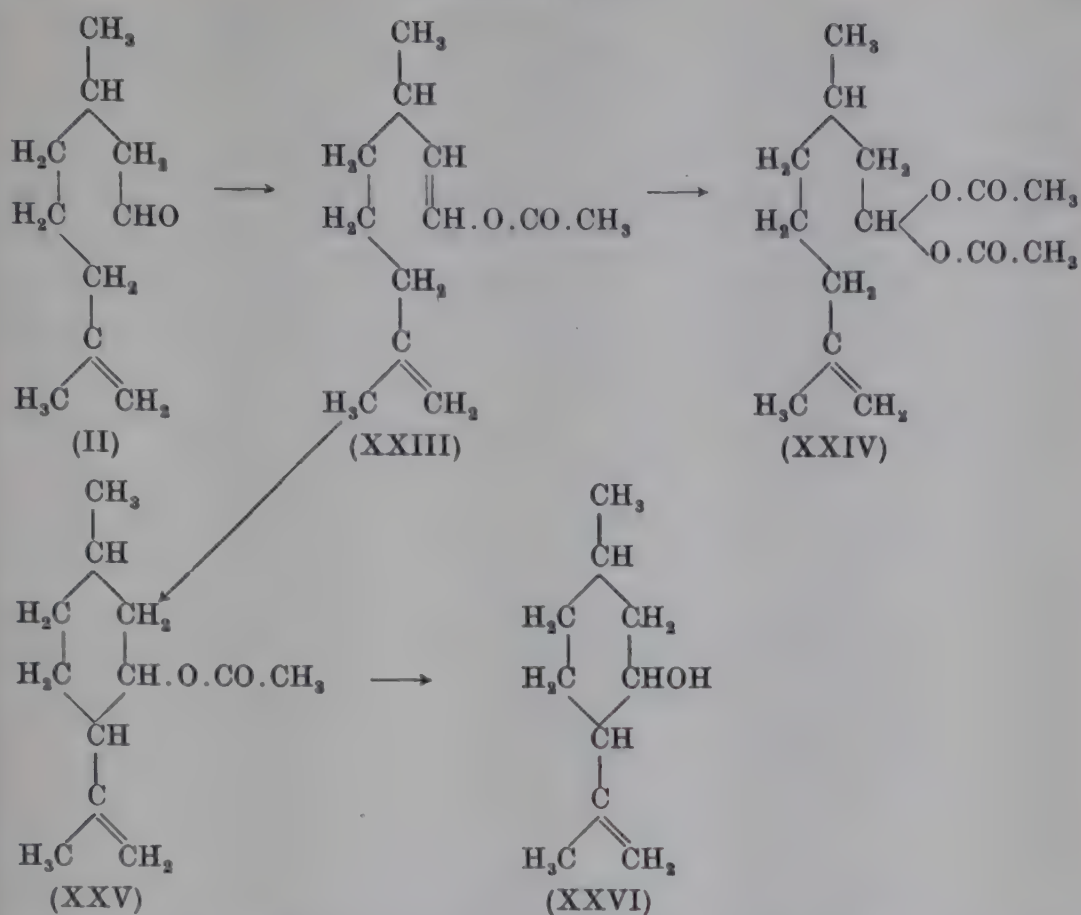
* Ber. 1891, 24, 209.

† Rochussen, *J. pr. Chem.* 1922 [ii], 105, 125; Schimmel's Report, 1909, April, p. 94; 1910, April, p. 20; Gliichitch and Müller, *Chim. et Ind.* 1928, 19, p. 479; Uchida, *Chem. Zentr.* 1928, II, 2296; Penfold, Ramage and Simonsen, *J. Proc. Roy. Soc. New South Wales*, 1935, 68, 80.

‡ Ber. 1909, 42, 4814; *J. Russ. Phys. Chem. Soc.* 1911, 43, 609.

§ Ber. 1896, 29, 913; 1897, 30, 27.

|| *Ibid.* 1909, 42, 2016.



Bogert and Hasselström* have shown that the direct conversion of citronellal into isopulegol occurs without solvent, under the influence of ultra-violet light; furthermore, under these conditions the enol acetate (XXIII) is converted into isopulegol acetate (XXV). Activated carbon is also an effective catalyst for the cyclisation.†

It has been mentioned already that, although citronellol on oxidation with chromic acid mixture gives citronellal, the yield is poor owing to the side reactions which occur. These reactions are mainly in the direction of the formation of cyclic derivatives owing to condensation of the citronellal by the acid in the oxidising mixture. Tiemann and Schmidt considered isopulegol to be the main product of the reaction, but Barbier and Bouveault‡ made the important observation that *menthone* (XXVII) was also formed, an observation which was fully confirmed by the later work of Bouveault.§ The reaction may be

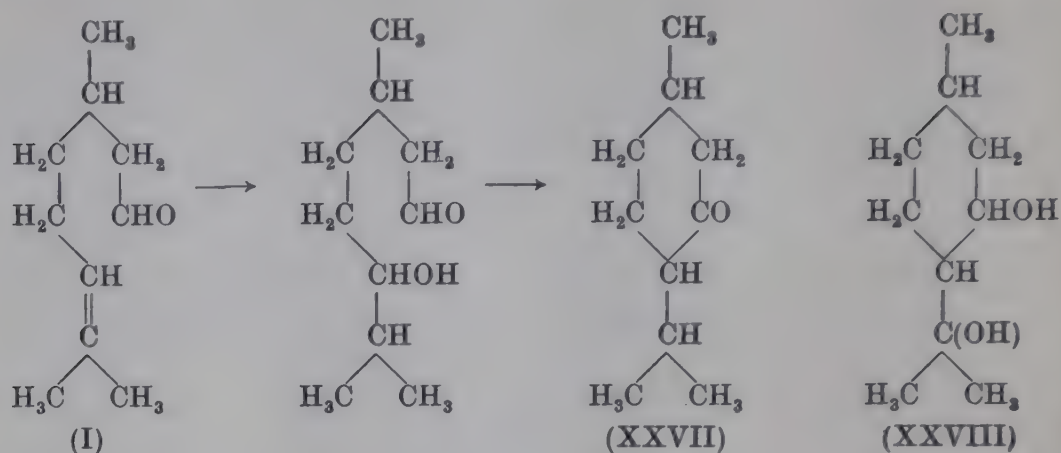
* *J. Amer. C.S.* 1930, 52, 4093.

† Kimura, *Bull. Chem. Soc. Japan*, 1935, 10, 330.

‡ *Compt. rend.* 1896, 122, 737.

§ *Bull. Soc. chim.* 1900 [iii], 23, 463.

represented as taking place in accordance with the following scheme:



Cyclic derivatives are also formed by the action of dilute acids on citronellal. By the action of dilute sulphuric acid (5 per cent.) Barbier and L  ser* obtained *isopulegol* and *menthoglycol*, *p-menthane-3:8-diol* (XXVIII), a hydrocarbon or mixture of hydrocarbons being also formed. Prins† has shown that *isopulegol* and its derivatives are obtained by the action of formic acid (85–90 per cent.) and by phosphoric acid (80 per cent.), whilst the conclusions of Barbier and L  ser have been confirmed and extended by other workers.* Of interest also is the action of phosphorus pentoxide, which has been investigated by Dodge.‡ A crystalline compound of the formula $C_{10}H_{19}O_4P$ is formed, which is probably a derivative of *isopulegol*. It is possible that sulphur dioxide, which reacts very vigorously with citronellal,§ may yield a compound of a similar type.

* *Compt. rend.* 1897, **124**, 1308.

† *Chem. Weekblad*, 1916, **14**, 627.

‡ Horiuchi *et al.*, *Mem. Coll. Sci. Kyoto*, 1928, **2** (A), 171; *Bull. Chem. Soc. Japan*, 1939, **14**, 501; *D  uvre, Bull. Soc. chim.* 1933 [iv], **53**, 27, 170.

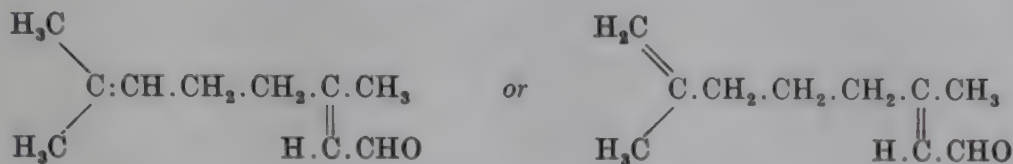
§ *Amer. Chem. J.* 1890, **12**, 553; *J. Amer. C.S.* 1915, **37**, 2756.

|| Tiemann, *Ber.* 1898, **31**, 3305.

CITRAL

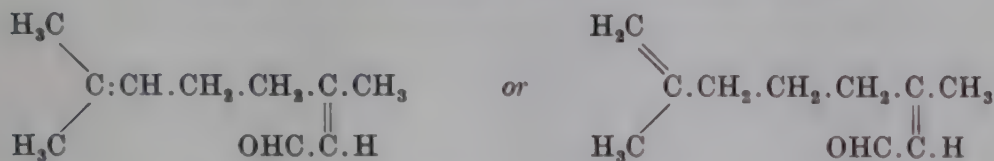
CITRAL a (GERANIAL)

(cis-2:6-Dimethyl- $\Delta^{2:6}$ -octadien-8-al or
cis-2:6-Dimethyl- $\Delta^{1:6}$ -octadien-8-al)



CITRAL b (NERAL)

(trans-2:6-Dimethyl- $\Delta^{2:6}$ -octadien-8-al or
trans-2:6-Dimethyl- $\Delta^{1:6}$ -octadien-8-al)



The aldehyde, *citral*, $\text{C}_{10}\text{H}_{16}\text{O}$, is the most important member of the group of aliphatic terpenes, possessing properties of great scientific interest and also being of considerable technical importance. As will be seen from the sequel, citral, as it occurs in nature, is a mixture of at least two and probably four isomerides, which are designated citral *a* and citral *b*.

Citral occurs in a very large number of essential oils,* and forms the principal constituent (about 80 per cent.) of lemon grass oil (from *Cymbopogon flexuosus* Stapf). The aldehyde was first separated from the oil of *Backhousia citriodora* by Bertram,† who gave it the correct empirical formula $\text{C}_{10}\text{H}_{16}\text{O}$, and showed it to be either a ketone or an aldehyde.

In 1890, Semmler* made the important observation that geraniol gave on gentle oxidation an aldehyde, $\text{C}_{10}\text{H}_{16}\text{O}$, which on further oxidation yielded an acid, $\text{C}_{10}\text{H}_{16}\text{O}_2$. He recognised that this aldehyde, *geranial*, was identical with the aldehyde which had been obtained previously from a number of essential oils and he suggested that it belonged to the aliphatic series. In

* For a detailed list see Gildemeister and Hoffmann, *Die Ätherischen Öle*, 3rd ed., I, 509.

† Schimmel's Report, 1888, April, p. 17.

* Ber. 1890, 23, 2965, 3556.

the same year Dodge* separated an aldehyde, which he called *citral*, from lemon grass oil and he showed that it reacted abnormally with sodium bisulphite solution. He found that it was optically inactive, the slight observed activity being due to impurities. In the following year Semmler† showed geranial and citral to be identical, and since then the presence of the aldehyde has been established in a number of essential oils from which it is best separated by means of its crystalline compound with sodium bisulphite.

As has been mentioned already (p. 41), not only can citral be obtained by the oxidation of geraniol, but also by the oxidation of the tertiary alcohol, linalool. Its formation from the latter alcohol led to a prolonged controversy between Barbier and his school on the one hand and Tiemann and Semmler on the other. This controversy is now only of historic interest and need not be considered further. Of great importance, however, was the discovery of Barbier and Bouveault‡ that the citral from lemon grass oil was not homogeneous, but that it gave two *semicarbazones*. This was fully confirmed by the subsequent investigations of Tiemann and Krüger,§ and Stiehl,|| and methods were devised for the separation of the isomeric aldehydes, which were designated citral *a* and citral *b*.

Citral *a*, which forms the major part (approximately 90 per cent.) of the aldehyde fraction of lemon grass oil, is most readily separated from citral *b* by the sodium bisulphite method suggested by Tiemann;¶ it yields a *semicarbazone* crystallising in needles, m.p. 164°. According to Zeitschel** it is also obtained, almost free from citral *b*, by the oxidation of geraniol. Citral *b* is most readily isolated by taking advantage of Tiemann's observation†† that citral *a* reacts much more readily with cyanoacetic acid than does citral *b*. Citral *b* has constants differing slightly from those of citral *a*, whilst the *semicarbazone* crystallises in leaflets, m.p. 171°. It is obtained nearly free from citral *a* by the oxidation of nerol (p. 53).

* *Amer. Chem. J.* 1890, **12**, 553.

† *Ber.* 1891, **24**, 201.

‡ *Compt. rend.* 1894, **118**, 983, 1050; 1895, **121**, 1159; 1896, **122**, 393.

§ *Ber.* 1898, **31**, 820.

|| *J. pr. Chem.* 1898 [ii], **58**, 51; 1899 [ii], **59**, 497.

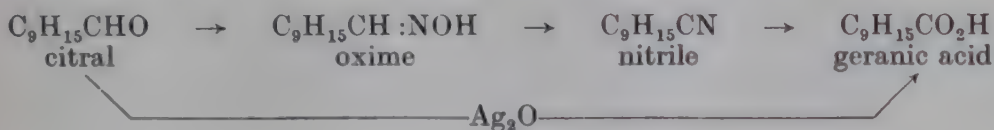
¶ *Ber.* 1899, **32**, 117.

** *Ibid.* 1906, **39**, 1787.

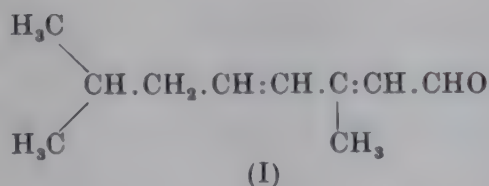
†† *Ibid.* 1900, **33**, 880.

The evidence bearing on the constitution of geraniol and nerol has been given already in some detail (pp. 42, 53), and since citral *a* and *b* are the aldehydes corresponding to these primary alcohols it will be possible to condense somewhat the discussion of the constitution of the aldehydes.

As is to be anticipated from the presence of an aldehydic group and two ethylenic linkages, citral* is very readily attacked by oxidising agents. By the action of ammoniacal silver oxide Semmler† obtained an acid, *geranic acid*, $C_{10}H_{16}O_2$, a result which first established the presence of an aldehydic group, and this acid was subsequently prepared in a better yield by Tiemann and Semmler‡ by the conversion of *citraloxime* into the *nitrile* of geranic acid, from which the acid was obtained on hydrolysis. Geranic acid is an oil, b.p. $153^\circ/13$ mm., d^{20}_D 0.964, n_D 1.4797. These reactions are shown by the scheme



On dehydration citral passes very readily into *p*-cymene, thus establishing the relative positions of the methyl and *isopropyl* groups, and this led Semmler§ in 1891 to suggest that citral was most probably represented by formula (I).



Shortly afterwards Tiemann and Semmler|| proved this formula to be incorrect, since they found that citral, on oxidation with dilute potassium permanganate followed by chromic acid mixture, gave acetone, levulinic and oxalic acids. They suggested that citral was represented by formula (II), the oxidation proceeding in accordance with the scheme given on p. 86.

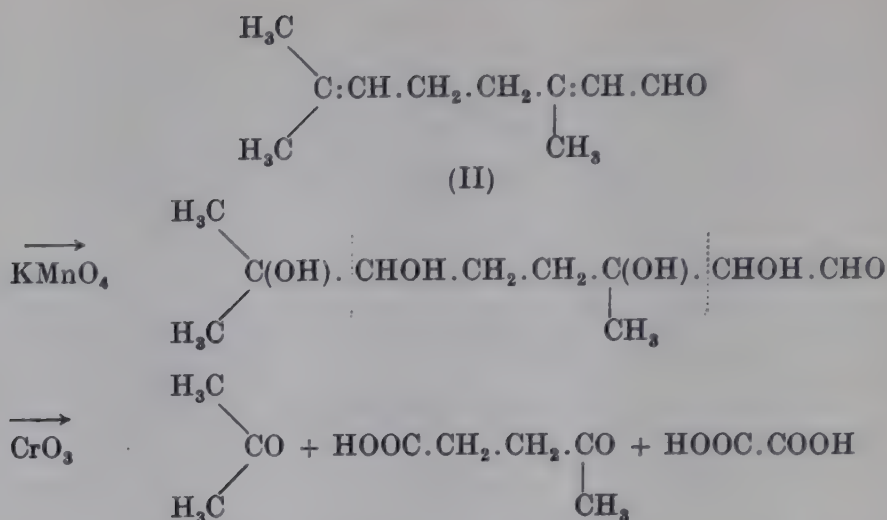
* Unless otherwise mentioned the term citral refers to the natural aldehyde, a mixture of citral *a* and citral *b*.

† *Ber.* 1890, **23**, 2965, 3556.

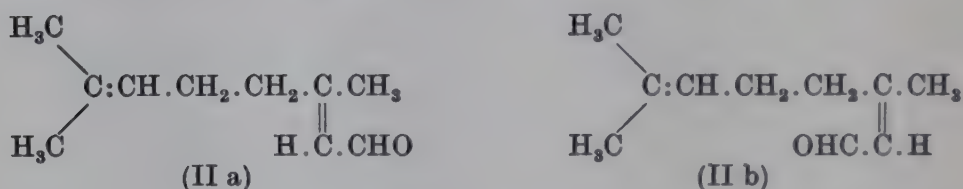
§ *Ibid.* 1891, **24**, 205.

‡ *Ibid.* 1893, **26**, 2717.

|| *Ibid.* 1895, **28**, 2132.



This formula would account for the existence of two citrals, citral *a* and citral *b*, since these could be the *cis-trans*-isomerides (II a) and (II b), a suggestion first advanced by Tiemann.



Other formulae, later shown to be incorrect, were suggested by Barbier and Bouveault* and by Stiehl.†

Additional evidence in support of Tiemann and Semmler's formula was soon forthcoming. In 1897 Verley‡ made the important observation that citral on digestion with alkali gave *methylheptenone* (IV) and acetaldehyde, hydrolytic fission taking place at the ethylenic linkage adjacent to the aldehydic group; whilst Barbier and Léser§ found that, when citral was oxidised with chromic acid, geranic acid (III), methylheptenone (IV) and *methylheptenonecarboxylic acid* (VI) were obtained. The latter acid is probably formed from the intermediate cyclic alcohol¶ (V) (see p. 87).

It is convenient to mention here the earlier work of Barbier and Bouveault,‡ in which they showed that geranic acid could

* *Compt. rend.* 1894, **118**, 983, 1050; 1895, **121**, 1159; *Bull. Soc. chim.* 1896 [iii], **15**, 594.

† *J. pr. Chem.* 1898 [ii], **58**, 93.

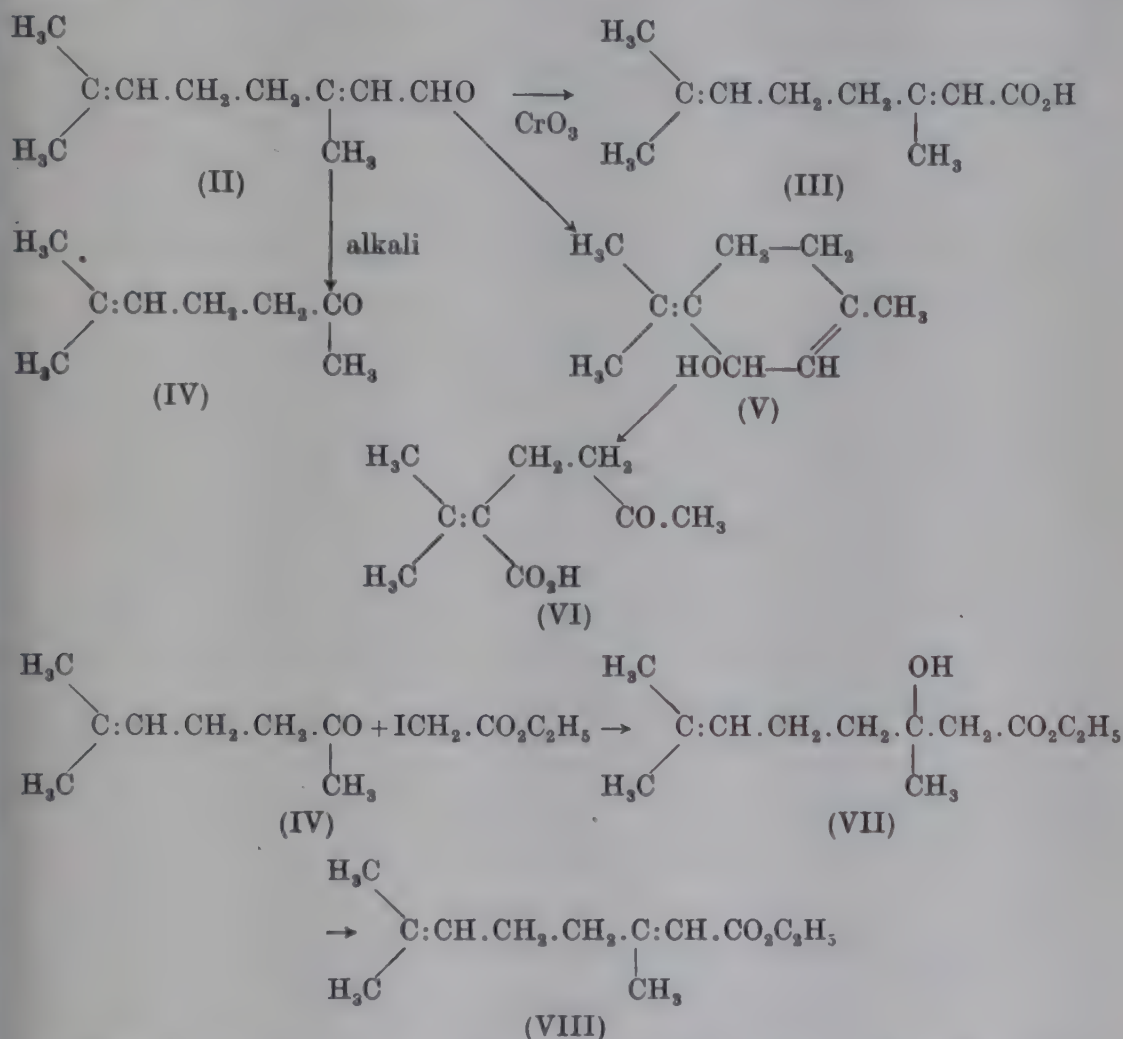
§ *Ibid.* p. 590.

‡ *Compt. rend.* 1896, **122**, 393.

* *Bull. Soc. chim.* 1897 [iii], **17**, 175.

¶ Tiemann and Semmler, *Ber.* 1895, **28**, 2135.

be prepared synthetically from methylheptenone by condensation of the ketone with ethyl iodoacetate in the presence of zinc. *Ethyl hydroxydihydrogeranate* (VII), the product of the reaction, gave on dehydration with acetic anhydride *ethyl geranate* (VIII), from which geranic acid (III) was obtained on hydrolysis, identical in all respects with that formed by the oxidation of citral.



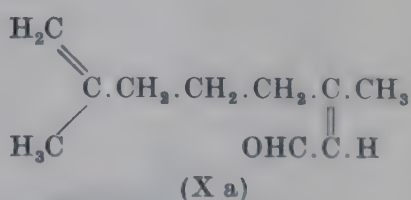
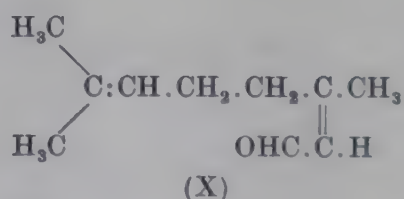
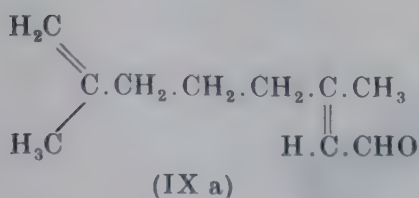
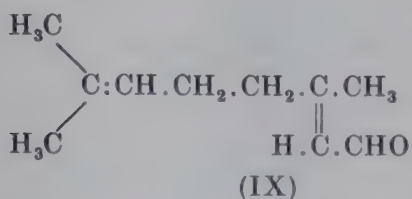
This synthesis was shortly afterwards confirmed by Tiemann,* who used ethyl bromoacetate in place of ethyl iodoacetate, and he showed also that when the calcium salt of geranic acid was distilled with calcium formate citral was obtained. Since methylheptenone has been synthesised by several methods,† this preparation of citral is a complete synthesis.

* Ber. 1898, 31, 828.

† Barbier and Bouveault, Compt. rend. 1896, 122, 1423; Verley, Bull. Soc. chim. 1897 [iii], 17, 175; Ipatiev, Ber. 1901, 34, 594.

The oxidation of citral with ozone has been studied by Harries and his collaborators.* The results obtained by them afforded a complete confirmation of the conclusion that citral *a* and citral *b* were stereoisomerides. On ozonolysis they both yielded the same products—acetone, levulinaldehyde and probably glyoxal. Grignard, Dœuvre and Escourrou† have reinvestigated this oxidation and have shown that both acetone and form-aldehyde are formed, the yield of the ketone indicating that the citral oxidised contained approximately 93 per cent. of a citral represented by formula (II). This was confirmed by an examination of the constitution of the methylheptenone formed on hydrolysis, which, like the parent aldehyde, gave a yield of acetone corresponding with a 93 per cent. content of the $\Delta^{2:6}$ -ketone (IV).

A critical survey of these experimental results would appear to leave no doubt that citral *a* and citral *b* are *cis-trans*-isomerides. In view of the relationship of citral *a* to geraniol and citral *b* to nerol their configuration is also established, citral *a* being the *cis*- and citral *b* the *trans*-isomeride. It is also clear from the experiments mentioned above that neither citral *a* nor citral *b* can be regarded as completely homogeneous, a conclusion supported by the experiments of Grignard and his collaborators,‡ on the constitution of geraniol. Citral *a* must therefore be regarded as a mixture of the two aldehydes represented by formulae (IX) and (IX a), whilst citral *b* would have formulae (X) and (X a).



* *Ber.* 1903, **36**, 1933; 1907, **40**, 2823; *Annalen*, 1905, **343**, 351.

† *Bull. Soc. chim.* 1924 [iv], **35**, 932.

‡ *Ibid.* 1925 [iv], **37**, 542, 546; 1927 [iv], **41**, 999; 1928 [iv], **43**, 1091.

It has been mentioned already in discussing the constitution of geraniol that this view is not shared by Dupont, Desreux and Dulou* or by Verley,[†] who offers another explanation of the experimental results and prefers to regard citral *a* and citral *b* as structural isomerides represented by (IX) and (IX a). The apparent homogeneity of the semicarbazones of citral *a* and citral *b*, and also of the condensation products formed with cyanoacetic acid (p. 100), cannot be regarded as conclusive evidence in view of the proved heterogeneity of citronellal semicarbazone (p. 74). It would not be without interest to examine the oxidation products of the semicarbazones of citral *a* and citral *b*.

The synthesis of citral from geranic acid has already been described (p. 87). This synthesis is of great importance since citral can readily be converted into geraniol and linalool, and it follows therefore that these alcohols can be prepared synthetically. Further, since geranic acid can be reduced to citronellic acid and this latter acid converted into citronellal and citronellol, a complete synthesis of these two substances follows.

Citral *a* is most conveniently obtained free from citral *b* by the method originally used by Tiemann, namely by the regeneration of the aldehyde from its sparingly soluble crystalline compound with sodium bisulphite, the corresponding derivative from citral *b* being readily soluble. The optimum conditions for the purification of citral *a* by this method have been described by Hibbert and Cannon.[‡] According to Auwers and Eisenlohr,[§] citral *a* has the following constants: b.p. 118–119°/20 mm., d^{20}_D 0.8898, n^{17}_D 1.4894.

Citral *b* is obtained free from citral *a* by taking advantage of the greater reactivity of the latter aldehyde with cyanoacetic acid. For the aldehyde prepared in this manner Auwers and Eisenlohr^{||} found the following constants: b.p. 117–118°/20 mm., d^{20}_D 0.8888, n^{20}_D 1.4891. As is to be anticipated from their constitution, both aldehydes show a marked exaltation in their molecular refraction owing to the conjugation of the ethylenic linkage and the carbonyl group.

* *Bull. Soc. chim.* 1937 [v], **4**, 2016.

† *Rev. des produits chim.* 1918, **21**, 352; *Bull. Soc. chim.* 1928 [iv], **43**, 854.

‡ *J. Amer. C.S.* 1924, **46**, 119.

§ *J. pr. Chem.* 1910 [ii], **82**, 116; 1911 [ii], **84**, 14.

|| *Ibid.* 1910 [ii], **82**, 116; 1911 [ii], **84**, 14.

When freshly distilled both citral *a* and citral *b* are colourless mobile oils with a characteristic smell, although, according to Verley, there is a marked difference between them. On exposure to the air citral is oxidised fairly rapidly and becomes yellow in colour. It has been shown by Berthelot and Gaudechon* that it is decomposed by the action of ultra-violet light with formation of carbon monoxide and hydrogen. The absorption spectrum of citral has been carefully studied by Bielecki and Henri.†

Citral can be readily characterised by the preparation of a number of derivatives and, since natural citral consists predominantly of citral *a*, derivatives of this aldehyde are, as a rule, most readily obtained pure. It may be identified (i) by the preparation of the *semicarbazones*, that from citral *a* having m.p. 164°, whilst that derived from citral *b* has m.p. 171°; (ii) by the condensation products formed with cyanoacetic acid, *a-citrylidenecyanoacetic acid*, having m.p. 122°, *b-citrylidenecyanoacetic acid*, m.p. 94°; and (iii) by the preparation of *a-citryl-β-naphthocinchonic acid*, m.p. 198–200°, which is obtained by the condensation of citral with β-naphthylamine in the presence of pyruvic acid. It will thus be seen that citral can be identified very readily, although, if citronellal is also present, careful recrystallisation of the derivatives may be necessary.

The reduction of citral has been studied by a number of workers since the pioneering experiments of Dodge and Tiemann,* who showed that it was converted into geraniol on reduction with sodium amalgam in a faintly acid solution. No experiments would appear to have been carried out on the separate reduction of citral *a* and citral *b*, so that it is not known whether the two aldehydes behave in the same manner and are reduced at equal rates. When reduced with zinc dust in acetic acid solution a *pinacone*, $C_{20}H_{34}O_2$, is formed.‡ The catalytic hydrogenation has been studied under widely varying conditions. With colloidal palladium as the catalyst, Skita^{||} showed *citronellal* and *citronellol* to be the main products of the reaction. Using platinum black, Vavon§ obtained 2:6-dimethyloctane and 2:6-dimethyloctan-8-ol, whilst Adams and Garvey,** with Adams' platinum catalyst,

* *Compt. rend.* 1910, 151, 1351.

† *Loc. cit.*

‡ *Ber.* 1909, 42, 1634.

** *J. Amer. C.S.* 1926, 48, 477.

† *Ber.* 1914, 47, 1701.

§ Verley, *Bull. Soc. chim.* 1899 [iii], 21, 412.

§ *Ann. chim.* 1914 [ix], 1, 169.

obtained *geraniol*, *citronellol* and 2:6-dimethyloctan-8-ol. Working under high pressure with a nickel catalyst Ipatiev* showed 2:6-dimethyloctane and 2:6-dimethyloctan-8-ol to be the main products, only the hydrocarbon being formed with a palladium catalyst under similar conditions. At a somewhat lower pressure with a nickel catalyst v. Braun and Kaiser† were able to obtain the saturated alcohol as the sole product. More recently Escourrou‡ has reduced citral at 190°, under diminished pressure with a nickel catalyst. He obtained as the sole product *dl*-citronellal, the *semicarbazone* of which had m.p. 80–81°, somewhat lower than the active form which melts at 84°. Law§ has attempted to reduce citral electrolytically but the results were not satisfactory and the only product identified was *geraniol*. As Neuberg and Kerb|| have shown, this alcohol is also obtained when citral is reduced with yeast.

According to Semmler,¶ in acetic acid solution citral takes up two molecules of bromine with formation of *tetrabromocitral*, a thick pale yellow oil, which decomposes rapidly on keeping with evolution of hydrogen bromide.

The pyrolysis of citral leads to the formation of a mixture of unsaturated hydrocarbons.**

Owing to the tendency for citral to undergo ring formation, additive compounds with the halogen acids have not been obtained. Cyclisation is also observed when citral is treated with dilute sulphuric acid. It is probable that the primary product is the *glycol* (XI), which loses water with formation of *p*-cymene or its derivatives.

The conversion of citral into *p*-cymene was first realised by Semmler,†† who used potassium hydrogen sulphate as the condensing agent. This method threw no light on the mechanism of the reaction. The experiments of Verley‡‡ were more informative; he found that citral, when treated with sulphuric acid in the presence of ethyl acetate, was converted into 1-methyl-4-isopropylidene-cyclohexen-3-ol (XII). This condensation is analogous

* Ber. 1912, 45, 3220.

† Ibid. 1923, 56, 2268.

‡ Bull. Soc. chim. 1928 [iv], 43, 1204.

§ J.C.S. 1912, 101, 1024.

|| Biochem. Z. 1918, 92, 111.

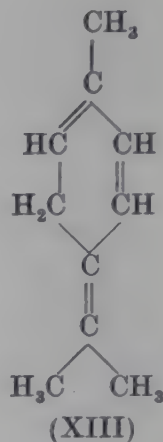
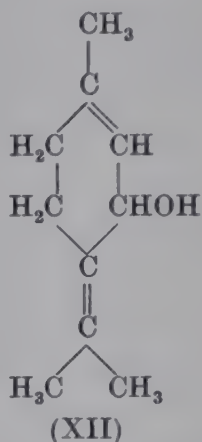
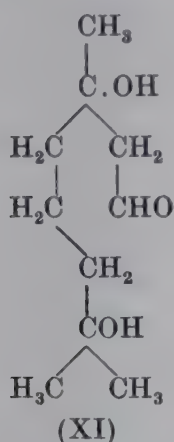
¶ Ber. 1891, 24, 202.

** Dœuvre and Desmule, Bull. Soc. chim. 1936 [v], 3, 196.

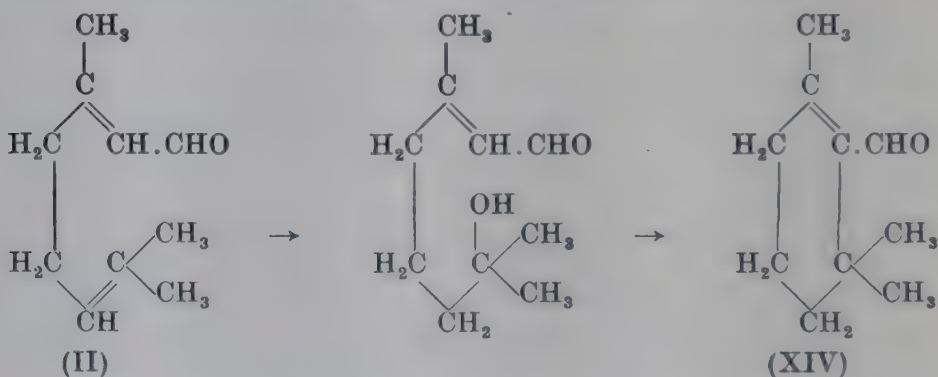
†† Ber. 1891, 24, 202.

‡‡ Bull. Soc. chim. 1899 [iii], 21, 408; see also Zeitschel and Schmidt, J. pr. Chem. 1932 [ii], 133, 370.

to the conversion of citronellal into *isopulegol* (p. 80). More recently, Horiuchi, Otsuki and Okuda* have shown that with 20 per cent. sulphuric acid a major product is $\Delta^{1:5:4(8)}$ -*p-menthatriene*, or *menogerene* (XIII), which is probably formed *via* the alcohol (XII). On further treatment with dilute sulphuric acid, it is isomerised into *p-cymene*.



In addition to yielding *p-cymene* and its derivatives, citral gives cyclic bodies of a different type known as the *cyclo-citrals* (XIV). The mechanism of this reaction is illustrated by the following scheme, a detailed consideration of the properties of these and allied substances being deferred (p. 116).



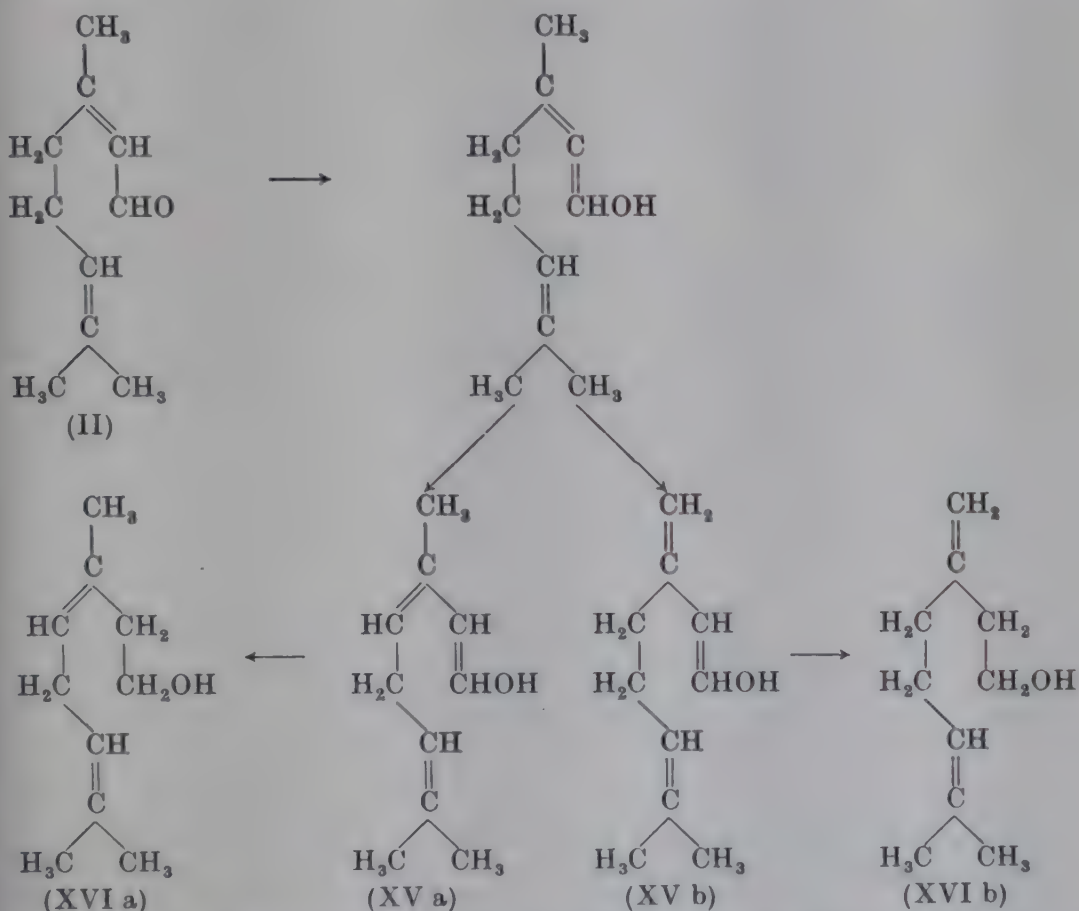
With perbenzoic acid[†] citral reacts to yield *citral monoxide*, $C_{10}H_{18}O_2$, an oil, b.p. $146-148^\circ/20$ mm., which on hydration gives a *glycollic aldehyde*, b.p. $141-142^\circ/24$ mm. The action of other oxidising agents on the aldehyde has been discussed already.

Owing to the tendency of citral to undergo cyclisation the preparation of the normal open chain derivatives affords some

* *Bull. Chem. Soc. Japan*, 1939, **14**, 501. † Prileschaev, *Ber.* 1909, **42**, 4814.

difficulty. When digested with acetic anhydride and sodium acetate it has been shown by Semmler and Schossberger* to yield the *acetate* of the *enolic* form of the aldehyde (XV a or b), which is an oil, b.p. 118–126°/10 mm., a small quantity of the diacetate being also formed. The reactions are illustrated by the scheme shown below.

It is not possible to hydrolyse the enolic acetate, but on reduction with sodium amalgam in methyl alcoholic solution in the presence of acetic acid it yields *isogeraniol*, which must be represented by either formula (XVI a) or (XVI b). It is an oil, b.p. 102–106°/10 mm., d^{20}_D 0.8874, n_D 1.4744, and it yields a *diphenylurethane*, m.p. 73°. It is not identical with either geraniol or nerol.



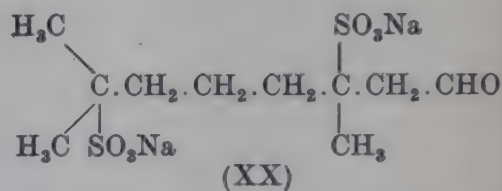
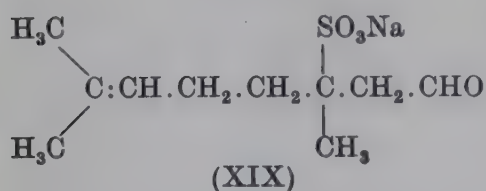
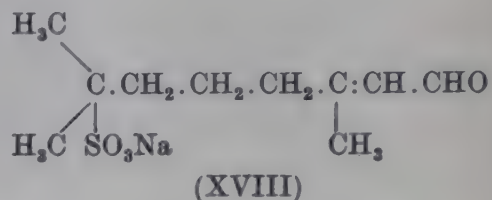
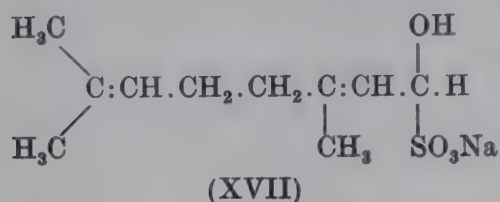
Citral shows very little tendency to form an acetal even under the effective conditions used by Haworth and Lapworth.†

In discussing the action of sodium bisulphite on citronellal (p. 78) it was seen that, in addition to the formation of the

* Ber. 1911, 44, 992.

† J.C.S. 1922, 121, 83.

normal compound by the interaction of the aldehyde group, addition took place also at the ethylenic linkage. With citral the reaction is even more complex owing to the presence of two ethylenic linkages. The action of sodium bisulphite on citral has been studied in great detail by Tiemann and his collaborators.* The normal bisulphite compound (XVII) is formed in a quantitative yield when citral is shaken with a sodium bisulphite solution containing some free acid.



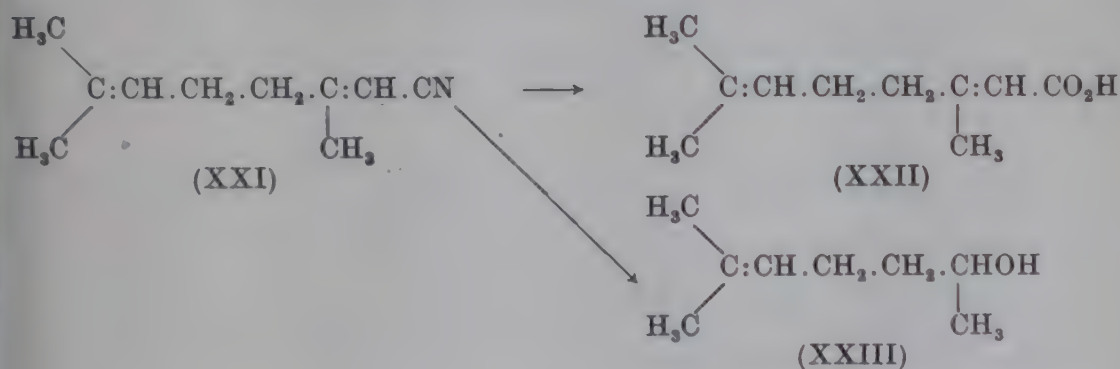
Such a solution is best prepared by adding a solution of crystalline sodium sulphite to slightly more than one molecular proportion of acetic acid. The salt is somewhat readily decomposed with liberation of citral, but it can be recrystallised from a solution of sodium bisulphite or from methyl alcohol containing a little acetic acid. Citral cannot be regenerated quantitatively, a loss of some 10–15 per cent. occurring on decomposition of the salt with alkali. The cause of this loss is not known, but it is possibly due to the formation of cyclic bisulphite compounds.

Two additive compounds are known containing two molecules of sodium bisulphite. One of these is obtained in a quantitative yield by treatment of the normal compound with an excess of sodium bisulphite for several hours, the solution being kept acidic. It is formed also when the normal compound is distilled in steam or digested with chloroform. The salt is crystalline but exceedingly hygroscopic; it contains a free aldehydic group since it reacts with phenylhydrazine, and it is possibly represented by formula (XX). Citral cannot be regenerated from it.

* *Ber.* 1893, **26**, 2710; 1898, **31**, 3297; compare Stiehl, *J. pr. Chem.* 1898 [ii], **58**, 78; 1899 [ii], **59**, 498; Romeo, *Gazzetta*, 1918, **48**, 1, 45; Hibbert and Cannon, *J. Amer. C.S.* 1924, **46**, 119.

A labile compound of the same composition is obtained when citral is shaken with a solution of sodium sulphite which is kept faintly alkaline during the reaction. This compound can be purified by crystallisation from methyl alcohol and contains a free aldehydic group since it yields a semicarbazone. By the action of acids it is converted into the stable derivative (XX) referred to above. The constitution of this substance is not known; when shaken with dilute alkali it yields a second mono-derivative containing a free aldehydic group represented probably by either formula (XVIII) or (XIX).

The oxime of citral *a* is an oil, b.p. 143–145°/12 mm., d^{20}_D 0.9386, n_D 1.5143, whilst that prepared from citral *b* has a slightly lower boiling-point, 136–138°/11 mm.* On treatment of the oxime with acetic anhydride the corresponding *nitrile* (XXI) results, an oil, b.p. 110°/10 mm., d^{20}_D 0.8709, n_D 1.4759, which on hydrolysis gives the acid *geranic acid* (XXII), a quantity of *methylheptenol* (XXIII) being formed simultaneously.



Both citraloxime and geranonitrile readily yield cyclic derivatives, which will be considered later.

Citralhydrazone and *citralphenylhydrazone* are oils; the decomposition products of the former have been studied by Kishner.†

Reference has been made already to the use of the *semicarbazones* of citral *a* and citral *b* as a means of identification. The semicarbazones were prepared first by Wallach and Naschold,* who obtained a mixture which they did not succeed in purifying. The separation of this mixture occasioned great difficulty and formed the subject of a prolonged series of investi-

* Tiemann and Semmler, *Ber.* 1893, **26**, 2716.

† *J. Russ. Phys. Chem. Soc.* 1913, **45**, 1779; 1918, **50**, 1.

* *Ber.* 1895, **28**, 1957.

gations by Tiemann and his collaborators,* and by Barbier and Bouveault.† As a result, it was established that ordinary citral, a mixture of citral *a* and citral *b*, gave two semicarbazones; the more sparingly soluble of these, which was the main product, crystallised in needles, m.p. 164°, whilst the second (6–10 per cent.) crystallised in leaflets, m.p. 171°. The relationship of these two semicarbazones was established by the subsequent work of Tiemann,‡ who showed that citral *a* gave the *semicarbazone*, m.p. 164°, whilst the *semicarbazone*, m.p. 171°, was derived from citral *b*. These results, which were confirmed by Barbier,§ have shown conclusively that the two semicarbazones are not *syn-anti*-isomerides but that they are derived from two isomeric aldehydes.

Amongst the most important reactions of citral are the condensations which it undergoes with substances containing a reactive methylene group. These reactions are not only of scientific interest but are also of technical importance, since they have led to the preparation of a number of substances of industrial value. These condensations are, as a rule, most satisfactorily carried out in alkaline media, since in the presence of acids cyclisation occurs.

The original impetus to the study of the condensation of citral and acetone was the isolation by Tiemann and Krüger|| from orris root, of a ketone, *irone*, thought to be C₁₃H₂₀O (see p. 130). These authors showed that when citral and acetone were condensed, a ketone, *pseudoionone*, with this molecular formula, was obtained, the reaction being formulated:



Pseudoionone¶ was described as an oil, b.p. 143–145°/12 mm., and unlike *irone* it possessed no characteristic odour. With sodium bisulphite it gave a crystalline compound, but the *oxime* and *phenylhydrazone* were oils. On treatment with semicarbazide acetate, a mixture of *semicarbazones* was formed from which a

* Ber. 2133; 1898, 31, 821, 2313, 3330.

† Compt. rend. 1895, 121, 1159; 1896, 122, 84, 844; Bull. Soc. chim. 1899 [iii], 21, 419, 423; compare Stiehl, J. pr. Chem. 1898 [ii], 58, 51; 1899 [ii], 59, 498.

‡ Ber. 1899, 32, 115; 1900, 33, 877.

§ Bull. Soc. chim. 1898 [iii], 19, 423.

|| Ber. 1893, 26, 2679.

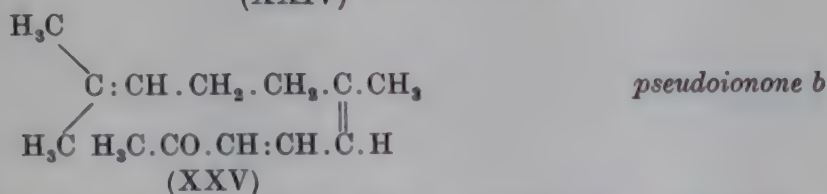
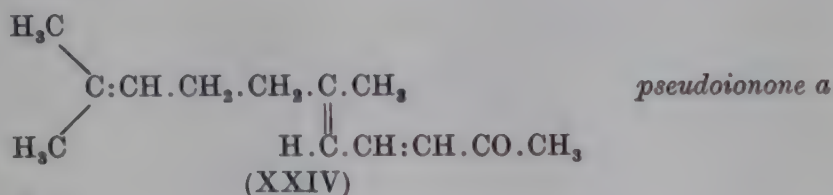
¶ Ibid. p. 2692.

pure substance, m.p. 142° , was separated. Like citral the ketone showed a very great tendency to undergo cyclisation.

The chemistry of pseudoionone was studied by numerous investigators,* but the next real advance in our knowledge of this ketone was the discovery by Tiemann† that citral *a* and citral *b* gave rise to isomeric pseudoionones. The ketone derived from citral *a* had b.p. $159-163^{\circ}/20$ mm., d^{20}_{20} 0.8954, n_D 1.5317, *semicarbazone*, m.p. 142° ; that from citral *b*, b.p. $146-150^{\circ}/15$ mm., d^{15}_{15} 0.898, n_D 1.5344, *semicarbazone*, m.p. $143-144^{\circ}$.

A mixture of the two semicarbazones melted indefinitely at $115-120^{\circ}$. It is interesting to note that there is no tendency for a semicarbazido-semicarbazone to be formed, probably owing to steric hindrance.

The isomeric pseudoionones may be represented by formulae (XXIV) and (XXV).



It does not appear to have been determined whether the pseudoionones are homogeneous or mixtures containing both the isopropylidene and isopropenyl groups.

The optimum conditions for the preparation of pseudoionone on a large scale have been systematically investigated and are described in the patent literature;‡ very complete details have been given by Hibbert and Cannon.§ The catalytic reduction of pseudoionone has been investigated by Skita,|| who has shown that, with colloidal palladium as the catalyst, *tetrahydropseudoionone*, b.p. $126-127^{\circ}/14$ mm., is formed and probably has the constitution represented by (XXVI).

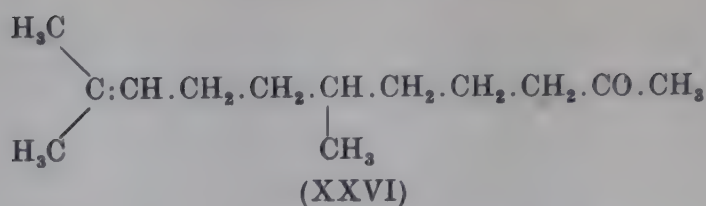
* *Inter al.*, Tiemann, *Ber.* 1898, **31**, 808; Doebner, *ibid.* 1888; Ziegler, *J. pr. Chem.* 1898 [ii], **57**, 493; Stiehl, *ibid.* 1898 [ii], **58**, 51.

† *Ber.* 1898, **31**, 2318; 1899, **32**, 827; 1900, **33**, 882.

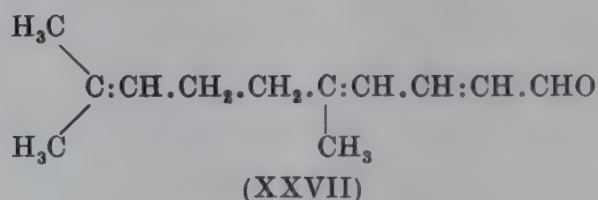
‡ *Inter al.*, Friedländer, *III*, 889; *G.P.* 122466, 127661, 130457.

§ *J. Amer. C.S.* 1924, **46**, 119; see also Russel and Kenyon, *Organic Syntheses*, 1943, **23**, 78.

|| *Ber.* 1912, **45**, 3315.



Homologues of pseudoionone derived from other ketones, such as methyl ethyl ketone and methyl propyl ketone* and the diketone, acetylacetone,† have been described. Condensation products with aldehydes have also received some attention, and interest in these compounds has been stimulated by the realisation of their potentialities as starting materials for the synthesis of polyenes and vitamin A.‡ With acetaldehyde, the main product is *citrylidene-acetaldehyde* (XXVII), b.p. 93–94°/0.02 mm., d_4^{20} 0.9346, n_D^{20} 1.5278 (*semicarbazone*, m.p. 170°, 2:4-dinitrophenylhydrazone, m.p. 132–133°).§



The product, b.p. 81–82°/0.15 mm., prepared by v. Braun and Rudolph|| by the reduction of the phenylimidochloride of citrylidene-acetic acid, may be a geometrical isomeride,¶ though the considerable variation in its physical constants from those of the product formed by direct condensation suggests a more fundamental difference in structure.

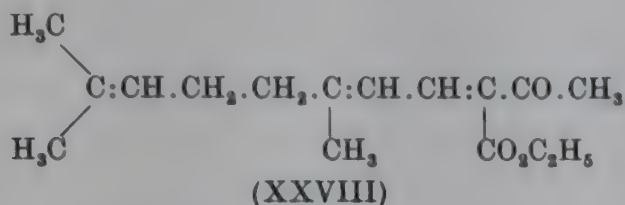
The condensation of citral with ethyl acetoacetate was first investigated by Verley,** pyridine being used as the condensing agent. He showed that the substance obtained was *ethyl citrylideneacetoacetate* (XXVIII) and that it could be readily converted into pseudoionone. This reaction has since been studied by Knoevenagel and his collaborators,†† who have examined the condensation of ethyl acetoacetate with both citral *a* and citral *b*

* G.P. 150771.

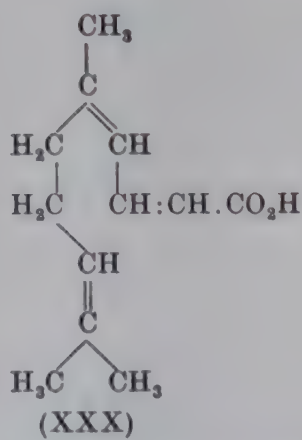
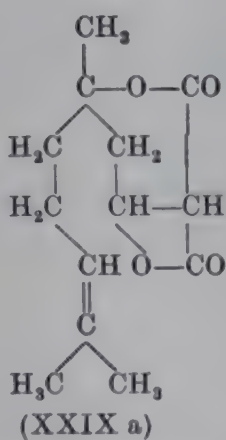
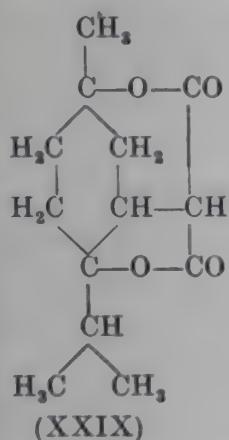
† G.P. 126960.

‡ Jones, *Ann. Reports C.S.* 1941, **38**, 170.§ Kuhn, Badstübner and Grundmann, *Ber.* 1936, **69**, 98; Batty, Burawoy, Heilbron, Jones and Lowe, *J.C.S.* 1937, 755; Barraclough, Batty, Heilbron and Jones, *ibid.* 1939, 1549.|| *Ber.* 1934, **67**, 1735.¶ v. Braun and Kurtz, *ibid.* 1937, **70**, 1009.** *Bull. Soc. chim.* 1899 [iii], **21**, 416.†† *Ber.* 1902, **35**, 392; *J. pr. Chem.* 1918 [ii], **97**, 288; 1921 [ii], **102**, 305.

and have prepared a number of cyclic derivatives which lie outside the scope of this work.



With ethyl malonate *ethyl citrylidenemalonate* is formed* and, by the condensation of citral with malonic acid in the presence of pyridine, a crystalline product (m.p. 186°) is obtained, which was originally assumed to be citrylidene-malonic acid.† The substance, however, contains no free carboxyl groups, and it is therefore formulated as a dilactone. Kuhn and Hoffer‡ favour the tricyclic structure (XXIX), whereas Vul'fson and Shemyakin§ consider that one lactone ring is of the β -type, and prefer the dicyclic structure (XXIX a). A substance with the latter formula would be expected to yield acetone on ozonisation, but this has not been detected.|| The substance is very readily decarboxylated to citrylidene-acetic acid (XXX) by distillation under reduced pressure in the presence of a trace of copper,¶ a reaction which is difficult to reconcile with either formula (XXIX) or (XXIX a).



Of considerable importance are the condensation products of citral *a* and citral *b* with cyanoacetic acid. This condensation

* Verley, *Bull. Soc. chim.* 1899 [iii], 21, 416.

† *Ibid.*

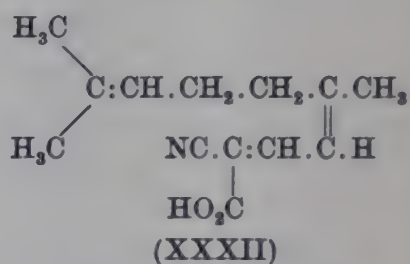
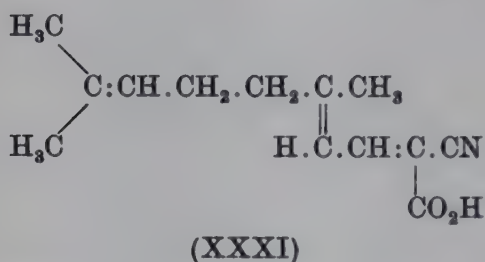
‡ *Ber.* 1931, 64, 1243.

§ *J. Gen. Chem. Russ.* 1943, 13, 436.

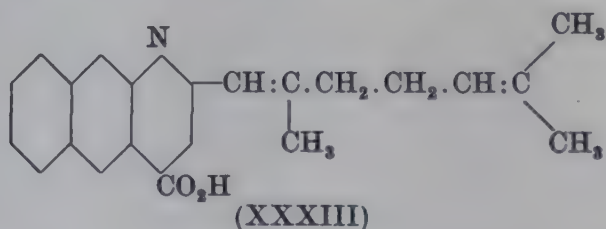
|| Batty, Burawoy, Heilbron, Jones and Lowe, *J.C.S.* 1937, 755.

¶ *Idem, ibid.*

was studied with very great care by Tiemann,* and, as has been mentioned already, resulted in the development of a method for the preparation of citral *b* in a pure state. In the presence of sodium ethoxide or sodium hydroxide, citral *a* condenses very rapidly with cyanoacetic acid, the reaction being complete in about three minutes. Citral *b*, however, condenses much more slowly and, if the alkaline solution be extracted after the first reaction is completed, practically pure citral *b* is obtained. On acidification of the alkaline solution, *a*-citrylidenecyanoacetic acid (XXXI), m.p. 122°, is precipitated. The isomeric acid (XXXII), m.p. 94°, can be prepared from citral *b* if the condensation is allowed to proceed for some considerable time. It is very much more soluble in benzene than the acid from citral *a*.



By the condensation of either citral *a* or citral *b* with β -naphthylamine in the presence of pyruvic acid, Doebner† prepared *citryl- β -naphthocinchonic acid* (XXXIII). This derivative, m.p. 200–201°, is useful for the identification of citral and it is interesting that both isomerides yield the same derivative.



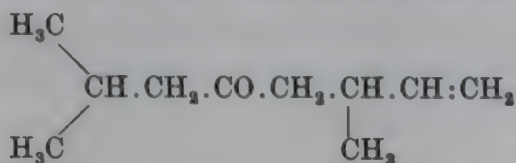
* Ber. 1898, 31, 3329; 1900, 33, 881; compare Andrews, Cristol, Lindenbaum and Young, J. Amer. C.S. 1945, 67, 715.

† Ber. 1894, 27, 352; 1898, 31, 3195.

CHAPTER IV

KETONES

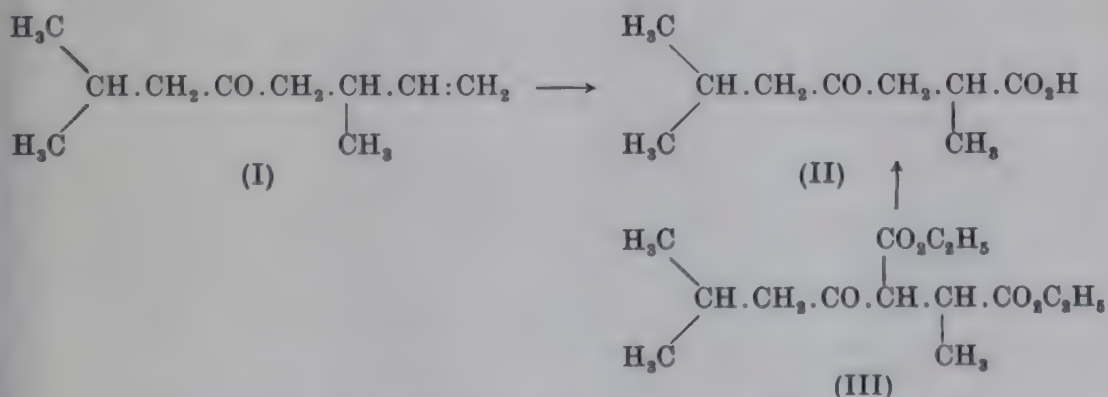
2:6-DIMETHYL- Δ^7 -OCTEN-4-ONE



The unsaturated ketone, 2:6-dimethyl- Δ^7 -octen-4-one, $\text{C}_{10}\text{H}_{18}\text{O}$, was separated by Jones and Smith* from the volatile oil present in the flowers of *Tagetes glandulifera*, a native of South America but growing also in Queensland.

The ketone, which was purified through the crystalline *semicarbazone*, is an oil, b.p. $185\text{--}186^\circ/760\text{ mm.}$, $d^{15.5^\circ} 0.8354$, $n_D^{20^\circ} 1.4295$, $[\alpha]_D + 1.5^\circ$. It can be characterised by the preparation of the *semicarbazone*, m.p. 92.5° , which crystallises from alcohol in needles. The *oxime* is an oil, b.p. $222^\circ/760\text{ mm.}$, $d^{15.5^\circ} 0.8778$, $[\alpha]_D + 2.4^\circ$.

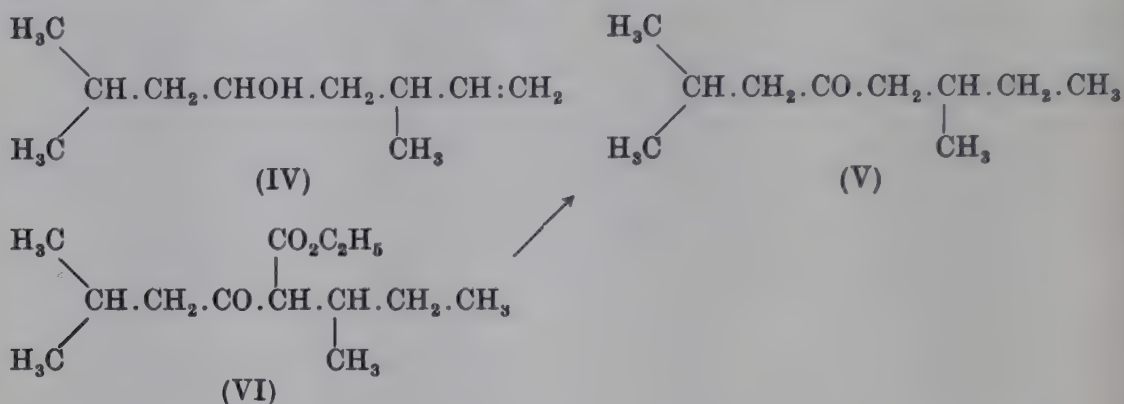
The constitution of the ketone (I) was determined by its oxidation with potassium permanganate in acetone solution, when, in addition to formic, acetic and *isovaleric* acids, a *ketonic acid*, β -isovaleryl- α -methylpropionic acid (II) was obtained. The ketonic acid is an oil, b.p. $169\text{--}171^\circ/25\text{ mm.}$, and yields a crystalline *semicarbazone*, m.p. 166° . The constitution of the acid has been proved by its synthesis by Jones,† who prepared it by the hydrolysis of the *ester* (III), which was obtained by the condensation of ethyl sodioisovaleryl acetate with ethyl α -iodopropionate.



* *J.C.S.* 1925, 127, 2530.

† *Ibid.* 1926, p. 2769.

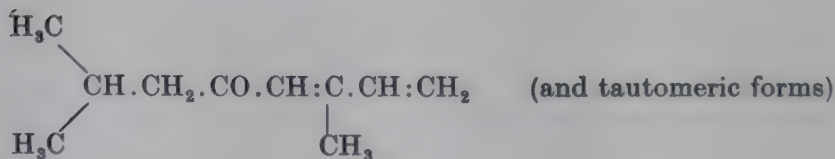
On reduction with sodium and alcohol the ketone yields the corresponding unsaturated secondary *alcohol*, 2:6-dimethyl- Δ^7 -octen-4-ol (IV), whilst on reduction with hydrogen at 180° with a nickel catalyst the saturated *ketone*, 2:6-dimethyloctan-4-one (V), is obtained. This ketone has been synthesised* by the condensation of ethyl sodioisovalerylacetate with *sec*-butyl iodide followed by hydrolysis of the *ketonic* ester (VI).



2:6-Dimethyl- Δ^7 -octen-4-one shows no tendency to cyclisation. It is not acted upon by sulphuric acid (20 per cent.) nor does it combine with sodium sulphite or sodium bisulphite. When warmed with sulphuric acid (70 per cent.) it undergoes profound decomposition, yielding amongst other products methyl ethyl ketone and methyl *isobutyl* ketone.

TAGETONE

(2:6-Dimethyl- $\Delta^{5:7}$ -octadien-4-one)



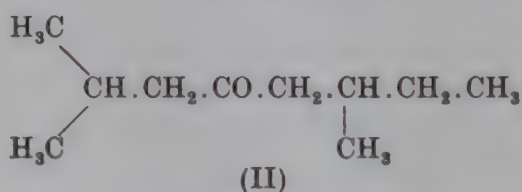
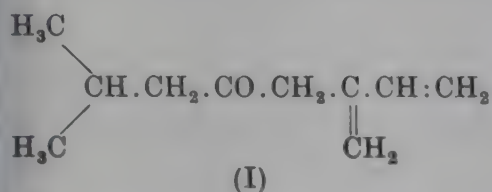
The ketone *tagetone*, $\text{C}_{10}\text{H}_{16}\text{O}$, which occurs in the oil derived from the flowers of *Tagetes glandulifera*, was first separated in 1925 by Jones and Smith.[†] It is found in the highest boiling fractions of the oil and, owing to its tendency to undergo resinification, it is somewhat difficult to obtain pure.

* J.C.S. 1926, p. 2769.

† Ibid. 1925, 127, 2530.

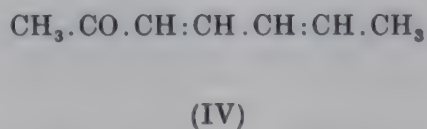
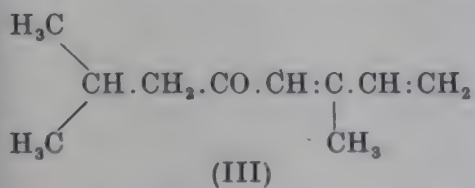
Tagetone is a pale yellow oil, b.p. *ca.* 205–210°/760 mm., 62°/3–4 mm., $d_{15.5}^{15.5}$ 0.8803, n_D^{20} 1.4895. No crystalline derivatives of the ketone have been prepared; the *oxime* is an oil, b.p. 126°/25 mm., $d_{15.5}^{15.5}$ 0.9207, n_D^{20} 1.4820, whilst the semicarbazone is resinous and cannot be obtained pure.

Consideration of its general properties, and investigation of the products formed on reduction and oxidation, appeared to indicate that tagetone was represented by (I). On reduction with hydrogen in the presence of platinum black, it is converted quantitatively into the saturated ketone, 2:6-dimethyloctan-4-one (II), the synthesis of which is described on p. 102; whilst on oxidation with potassium permanganate in alkaline solution



it yields isovaleric acid, oxalic acid, and a little acetic acid. On digestion with alcoholic potassium hydroxide, methyl isobutyl ketone is formed.

Reduction with aluminium isopropoxide gives the corresponding alcohol, *tagetol*, $\text{C}_{10}\text{H}_{18}\text{O}$, b.p. 55°/3 mm., $d_{15.5}^{15.5}$ 0.8766, n_D^{20} 1.4760,* which cannot be obtained by reduction of tagetone with sodium and alcohol. Jones† has shown that under the latter conditions the product is probably a dihydrotagetol, and he suggests that tagetone contains an ethylenic linkage in conjugation with the ketonic group and may be represented by (III).



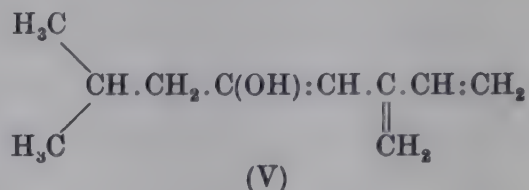
Support for this formulation is afforded by the presence of acetic acid in the oxidation products of tagetone, and also by the absorption spectrum of the ketone, which is very similar to that of *crotonylidene-acetone* (IV).‡

* Jones, *Univ. Queensland Papers, Dept. Chem.* 1939, 1, no. 11.

† *Proc. Roy. Soc. Queensland*, 1934, 45, 45.

‡ Jones and Lahey, *Univ. Queensland Papers, Dept. Chem.* 1942, 1, no. 22.

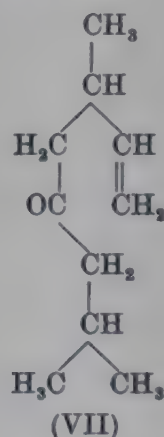
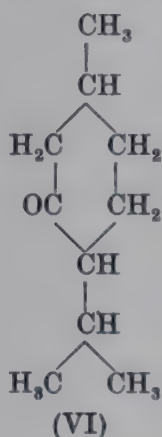
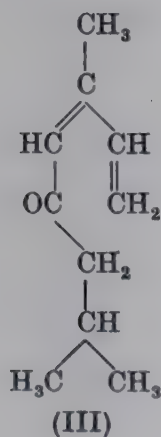
Tagetone reacts very readily with sodium with formation of red salts and this suggests that it is capable also of existing in the *enolic* form (V), which would account for its marked tendency to resinify.



It is probable, therefore, that tagetone is best represented as a tautomeric mixture of (I), (III) and (V).

Pinacones, and other products of unknown constitution, have been obtained* by reduction of tagetone with zinc and alkali, aluminium amalgam, etc.

The occurrence of the ketones tagetone (III) and 2:6-dimethyl- Δ^7 -octen-4-one (VII) (p. 101) in the same oil is of interest, since they may be regarded as fission products of the cyclic terpene ketones of the menthone (VI) type.

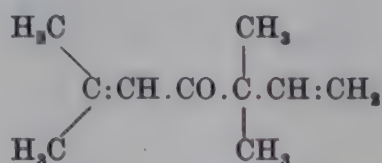
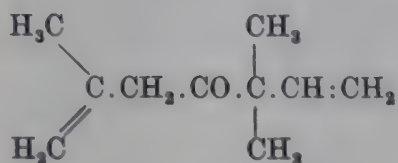


It is noteworthy that neither of the acyclic ketones shows any tendency to undergo cyclisation.

* Jones, *J.C.S.* 1926, 2768; *Proc. Roy. Soc. Queensland*, 1934, 45, 45.

ARTEMISIA KETONE AND ISO-ARTEMISIA KETONE

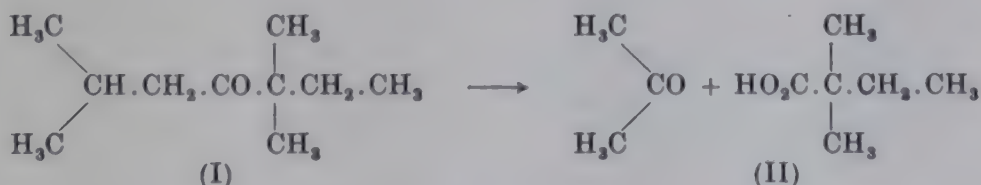
(2:5:5-Trimethyl- $\Delta^{1:6}$ -heptadien-4-one and
2:5:5-Trimethyl- $\Delta^{2:6}$ -heptadien-4-one)



A preliminary investigation of the oil from *Artemisia annua* L. by Imada* pointed to the presence in this oil of a ketone, $\text{C}_{10}\text{H}_{16}\text{O}$, yielding a *semicarbazone*, m.p. 95–96°. The ketonic fraction of this oil was subsequently studied by Asahina and Yoshitomi† and by Asahina and Takagi.‡

It was found by these authors that the appropriate fraction of the oil gave a mixture of two semicarbazones, which could be separated by fractional crystallisation. The more sparingly soluble of these, m.p. 95–96°, gave on hydrolysis *artemisia ketone*, b.p. 182°, d_4^{14} 0.8906, n_D^{18} 1.4695, whilst the more soluble, m.p. 70–72°, crystallised with water of crystallisation, the anhydrous *semicarbazone* melting at 103–104°, and gave on hydrolysis *iso-artemisia ketone*, b.p. 182–183°, d_4^{17} 0.8711, n_D 1.4188. Both ketones were optically inactive.

From their general properties the two ketones clearly belonged to the acyclic series and contained two ethylenic linkages. On catalytic hydrogenation they both yielded the same *tetrahydroketone*, b.p. 173°, d_4^{19} 0.8262, n_D 1.4242, which Asahina and Takagi considered to be 2:5:5-trimethylheptan-4-one (I), since on oxidation with chromic acid it gave $\alpha\alpha$ -dimethylbutyric acid (II) and probably also acetone.



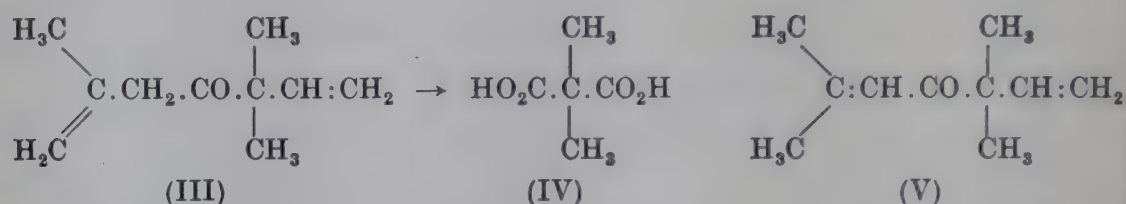
* *J. Pharm. Soc. Japan*, 1917, 420, 119.

† *Ibid.* 1917, 424, 1.

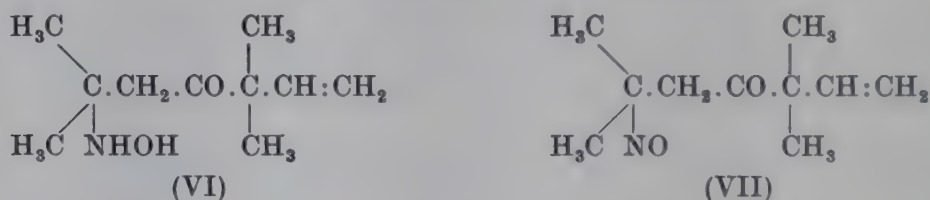
‡ *Ibid.* 1920, 464, 837.

This conclusion has been confirmed by Ruzicka, Reichstein and Pulver,* who have synthesised the ketone (I) by the condensation of $\alpha\alpha$ -dimethylbutyryl chloride with *isobutyl* zinc iodide.

The carbon structure having thus been determined, Asahina and Takagi oxidised the parent ketone, artemisia ketone, with potassium permanganate and obtained *dimethylmalonic acid* (IV). They suggest that the ketone should be represented by (III).



For the isomeric ketone, *iso*-artemisia ketone, which is formed also when artemisia ketone is treated with an alcoholic solution of sulphuric acid, formula (V) is suggested. With hydroxylamine it yields the *oximinoketone* (VI), and on oxidation this gives a crystalline substance, m.p. 64° , which behaves as a tertiary *nitroso*-compound, and is therefore formulated as (VII).†



The structure (III) assigned to artemisia ketone has been confirmed by Colonge and Dumont,‡ who have synthesised the ketone by the condensation of *isobutylene* and $\alpha\alpha$ -dimethyl- Δ^3 -butenoyl chloride in the presence of stannous chloride. Similarly, from *isobutylene* and $\alpha\alpha$ -dimethylbutyryl chloride, they have obtained *dihydroisoartemisia ketone*, b.p. 180° , $d_4^{15^\circ}$ 0.856, $n_D^{15^\circ}$ 1.4524.

* *Helv. Chim. Acta*, 1936, **19**, 646.

† Asahina and Takagi, *ibid.* 1937, **20**, 220; compare Ruzicka, *ibid.* p. 221.

‡ *Compt. rend.* 1945, **220**, 500.

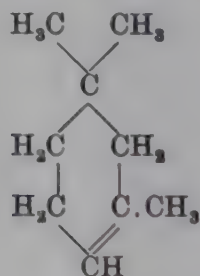
CHAPTER V

THE CYCLOGERANIOLLENES AND
THEIR DERIVATIVES

CYCLOGERANIOLLENES

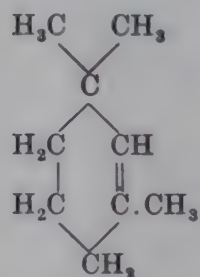
α -CYCLOGERANIOLLENE

(1:1:3-Trimethyl- Δ^3 -cyclohexene)



β -CYCLOGERANIOLLENE

(1:1:3-Trimethyl- Δ^2 -cyclohexene)



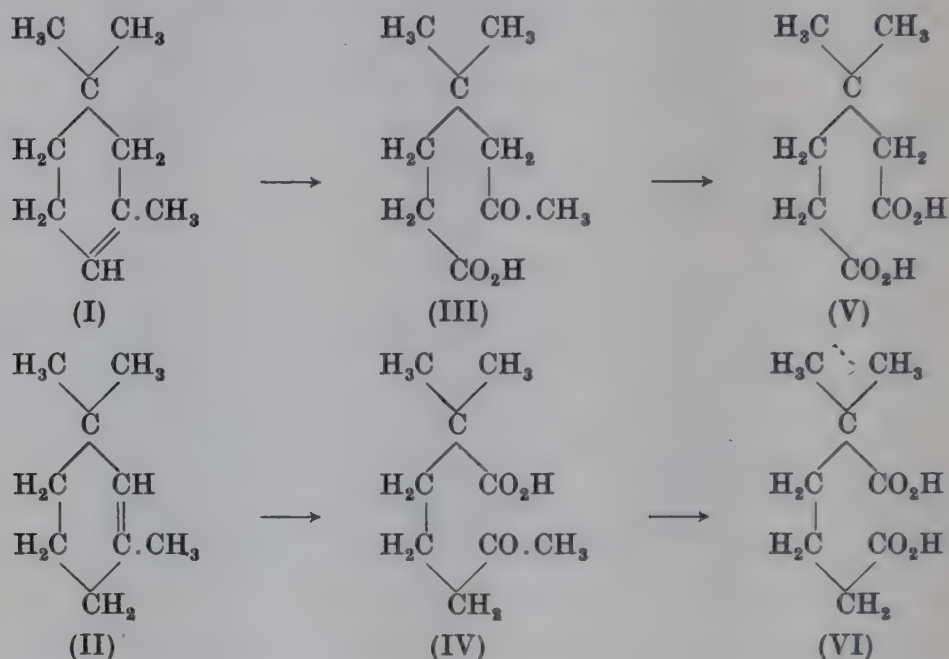
It was observed by Tiemann and Semmler* that when the olefinic hydrocarbon, *geraniolene* (p. 9), was warmed with sulphuric acid (60 per cent.) it was isomerised with formation of a cyclic hydrocarbon to which these authors gave the name *isogeraniolene*. The investigation of this hydrocarbon was continued by Tiemann,[†] who showed, by an examination of the products formed on oxidation, that it was not homogeneous.

When "*isogeraniolene*" was oxidised with potassium permanganate a mixture of *ketonic-acids* was obtained and these were separated by fractional crystallisation of their semicarb-

* *Ber.* 1893, 26, 2724.

[†] *Ibid.* 1900, 33, 3711.

azonas. The *ketonic acid* present in larger quantity (75 per cent.) was *isogeronic acid* (III), *geronic acid* (IV) forming the remaining 25 per cent. of the ketonic acid fraction. The constitution of the ketonic acids was proved by their oxidation respectively to $\beta\beta$ -dimethyladipic acid (V) and $\alpha\alpha$ -dimethyladipic acid (VI). It followed from these observations that *isogeraniolene* was a mixture of the two hydrocarbons represented by formulae (I) and (II), α -cyclogeraniolene (I) being the main constituent.

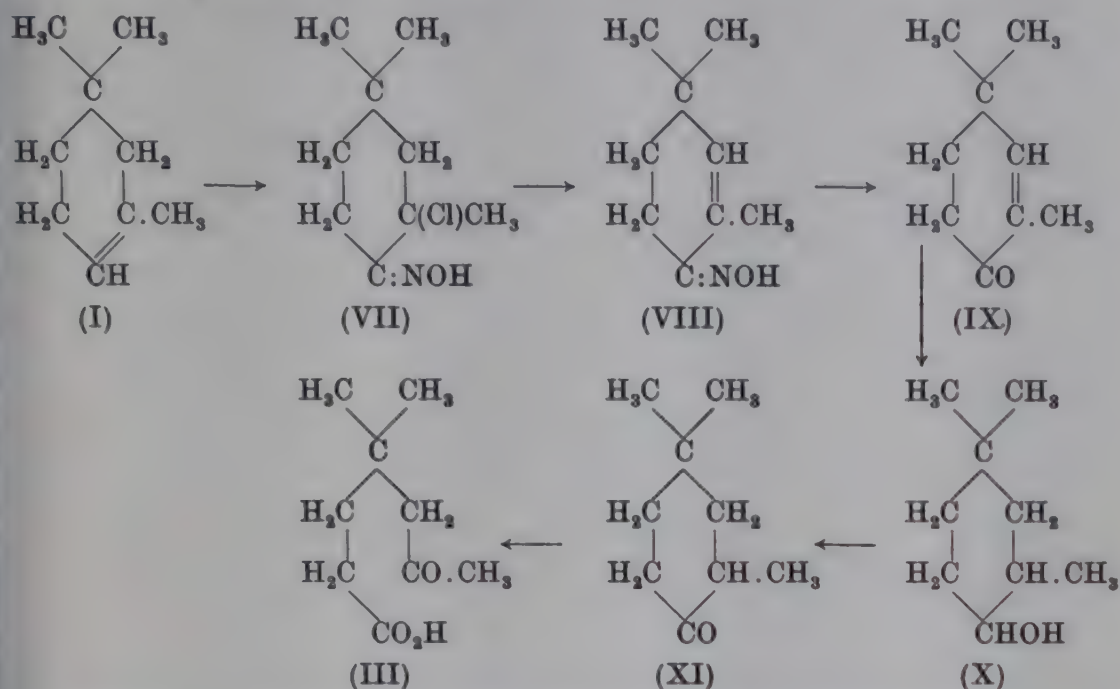


The constitution suggested by Tiemann received support from the investigations of Wallach and Franke.* These authors prepared the *cyclogeraniolenes* by the cyclisation of geraniolene with sulphuric acid ($d = 1.56$) at room temperature. They thus succeeded in obtaining a hydrocarbon consisting mainly of α -cyclogeraniolene, which was characterised by the preparation of a *nitrosate*, m.p. $102-104^\circ$, and a *nitrosochloride* (VII), probably a mixture, m.p. $100-120^\circ$. When either the nitrosate or the nitrosochloride was treated with alcoholic potassium hydroxide solution 4-oximino-1:1:3-trimethyl- Δ^2 -cyclohexene (VIII) was formed, which on hydrolysis yielded the corresponding *ketone* (IX).

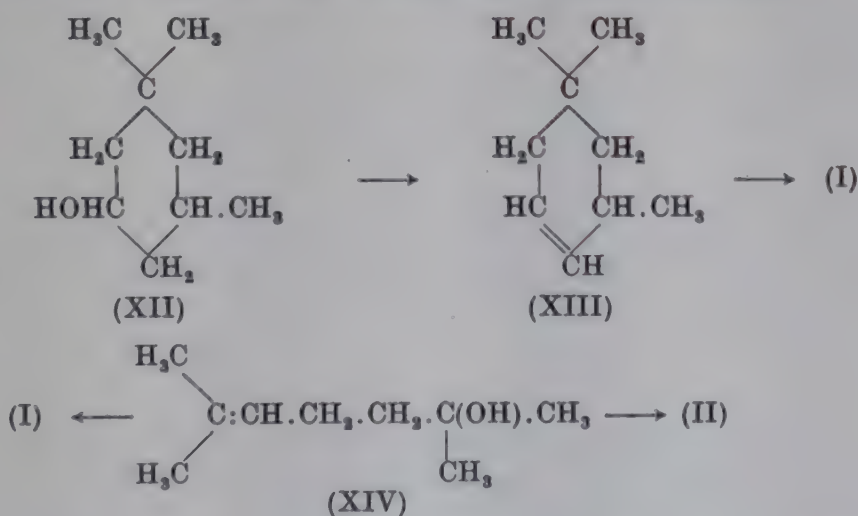
When the unsaturated ketone (IX) was reduced with sodium and alcohol it was converted into the saturated secondary

* *Annalen*, 1902, 324, 114.

alcohol, 1:1:3-trimethylcyclohexan-4-ol (X), which on oxidation gave 1:1:3-trimethylcyclohexan-4-one (XI), and this, on further oxidation, gave isogeronic acid (III).



At the same time, Wallach showed the hydrocarbon obtained by Knoevenagel* by the elimination of water from dihydroisophorol (XII) to be identical with α -cyclogeraniolene, the primary product (XIII) of the reaction undergoing isomerisation.

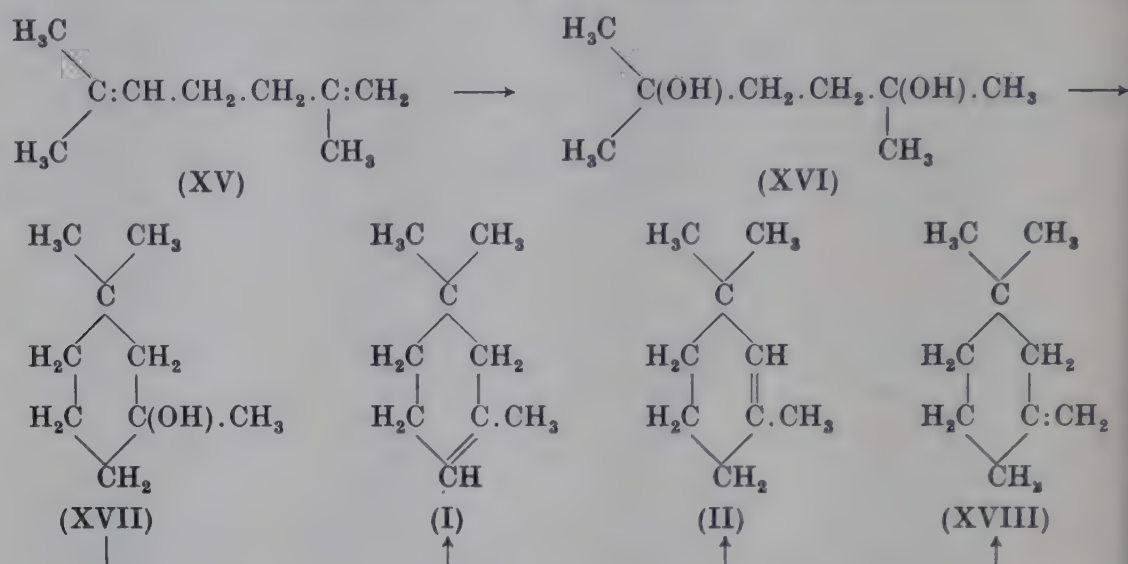


The cyclogeraniolenes were prepared also by Harries and Weil† by the dehydration of 2:6-dimethyl- Δ^2 -hepten-6-ol (XIV).

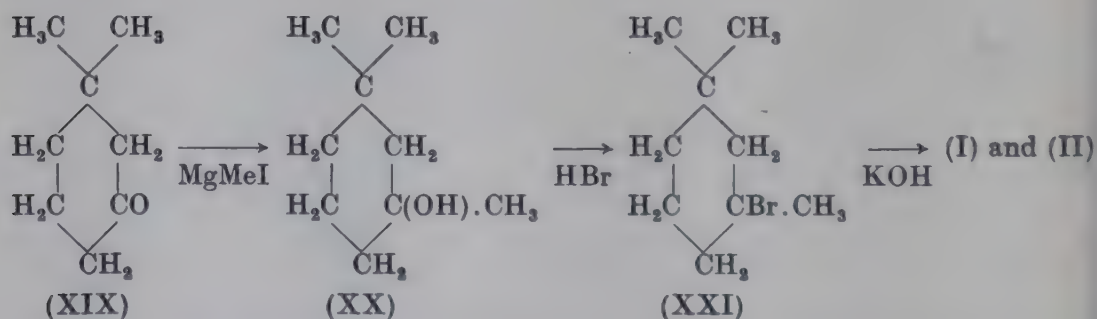
* *Annalen*, 1897, 297, 199.

† *Ber.* 1904, 37, 848.

Tiemann suggested that the conversion of geraniolene (XV) into the two *cyclogeraniolenes* was preceded by the formation of the *glycol* (XVI) and the cyclic *alcohol* (XVII), from which water could be eliminated in three ways, yielding (I), (II) and (XVIII).



This view of the mechanism of the reaction was supported by the experiments of Crossley and Gilling,* who showed that when the *alcohol* (XX), prepared by treatment of the *ketone* (XIX) with methyl magnesium iodide, was converted into the bromide (XXI), and hydrogen bromide removed by alcoholic potassium hydroxide solution, a mixture of the two *cyclogeraniolenes* was obtained.



Whilst the experiments of Tiemann and Wallach would appear to have shown conclusively that *cyclogeraniolene* is a mixture of the α - and β -forms [(I) and (II)], Escourrou† suggested subsequently that the main constituent is the γ -form (XVIII). This

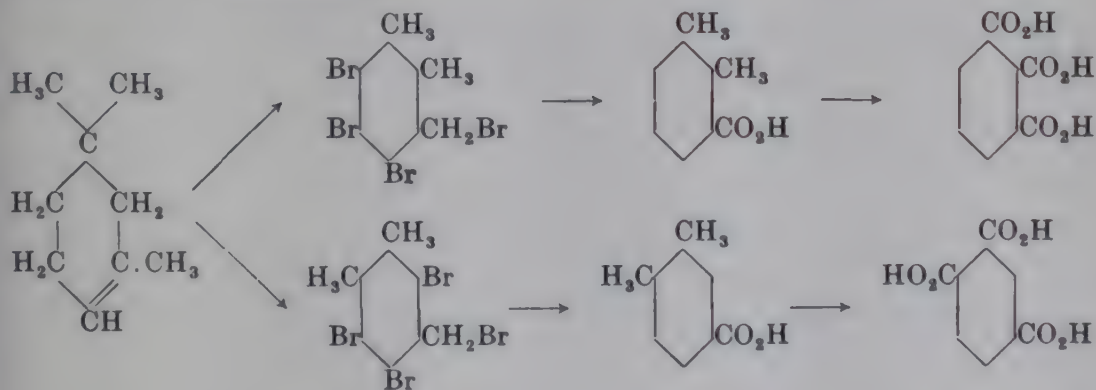
* *J.C.S.* 1910, **97**, 2218.

† *Bull. Soc. chim.* 1926 [iv], **39**, 1460; 1928 [iv], **43**, 1277.

conclusion is based on the fact that, when the hydrocarbon mixture is oxidised with ozone, formaldehyde is formed in large amount. In order to account for the formation of geronic and isogeronic acids on oxidation with potassium permanganate, Escourrou considered that a shift of the ethylenic linkage occurs in the presence of alkali. Whilst this may be regarded as a possibility, it would appear to be more probable that *cyclo-geraniolene* is in all cases a mixture of the α -, β - and γ -forms, in which one or the other predominates, depending upon the preparative method employed.

Cyclogeraniolene is a pleasant-smelling oil, b.p. $138-139^\circ$, $d_{20}^{20} 0.8072$, $n_D 1.4473$. Whilst the α -form has been characterised by the preparation of a crystalline nitrosochloride and nitrosate (p. 108) no crystalline derivatives of the β - or γ -forms have been described.

The exhaustive bromination of *cyclogeraniolene* was studied by Baeyer and Villiger,* who showed that a mixture of *bromotrimethyl benzenes* was formed by one of the *gem*-dimethyl groups wandering into the benzene ring. The bromotrimethyl benzenes were orientated by oxidation to the corresponding benzoic acids. The reactions involved are indicated by the following scheme, and it is interesting to note that the *gem*-dimethyl groups do not undergo bromination.



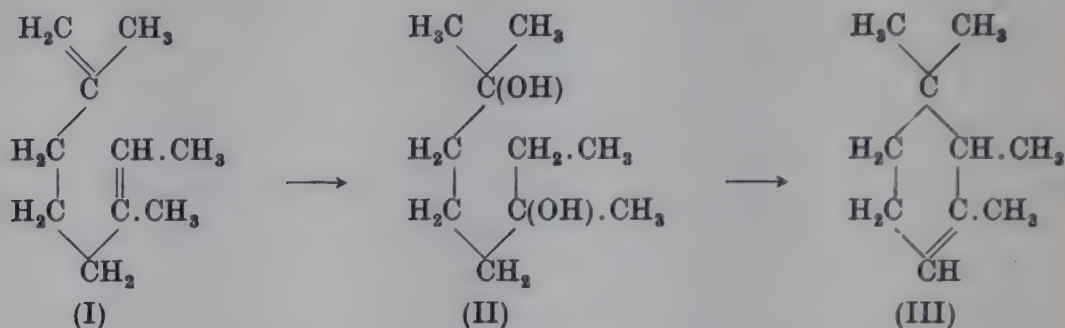
CYCLODIHYDROMYRCENE

Cyclodihydromyrcene, $\text{C}_{10}\text{H}_{18}$, was first prepared by Semmler† by treatment of dihydromyrcene (p. 12) with a solution of sulphuric acid in acetic acid. He described it as an oil, b.p. $169-$

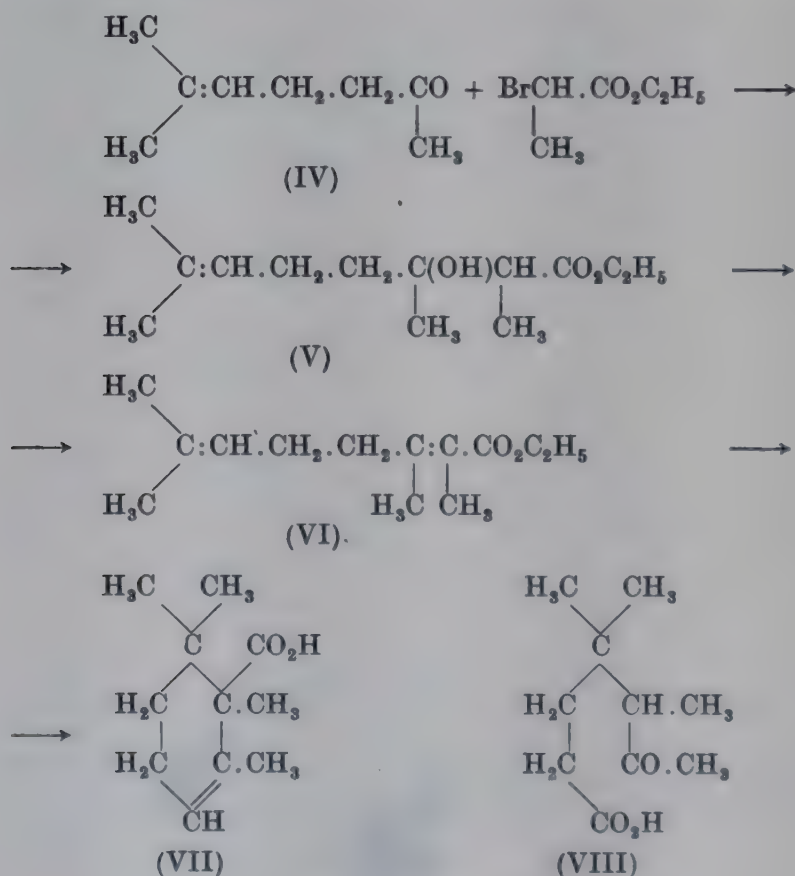
* *Ber.* 1899, 32, 2429.

† *Ibid.* 1894, 27, 2520; 1901, 34, 3126.

172°, d 0.828, n_D 1.462, and he suggested that it was represented by (III) being formed from dihydromyrcene (I) by dehydration of the *glycol* (II).



The hydrocarbon was subsequently prepared by Tiffeneau* from *ethyl methylgeranate* (VI), which he obtained synthetically from natural methylheptenone (IV) by condensation with ethyl- α -bromopropionate in the presence of zinc, the resulting *hydroxy-ester* (V) losing water on treatment with acetyl chloride to give ethyl methylgeranate (VI).

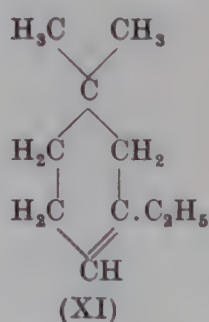
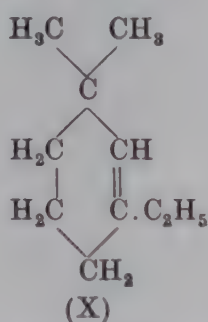
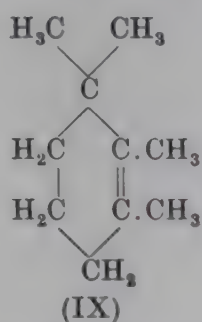
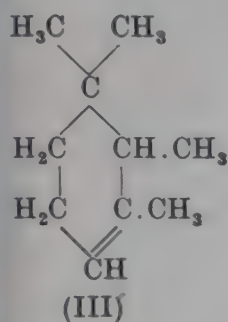


* *Compt. rend.* 1908, 146, 1153.

When the ester was heated with sulphuric acid it was converted into the cyclic acid (VII), b.p. 153–158°/11 mm., and this on distillation at the ordinary pressure lost carbon dioxide with formation of *cyclodihydromyrcene* (III). The constants of Tiffeneau's, hydrocarbon b.p. 168–170°, d^{14}_D 0.8325, n^{14}_D 1.460, differed somewhat from those of Semmler's.

According to Semmler *cyclodihydromyrcene* yields on oxidation a *ketonic acid*, $C_{10}H_{18}O_3$, which, if the above formula is correct, would be represented by (VIII), but definite evidence in support of this constitution is not available.*

Auwers and Moosbrügger† suggested that the hydrocarbon prepared by Semmler's method is very probably a mixture of the four hydrocarbons (III), (IX), (X) and (XI), all of which can theoretically be formed from the glycol (II).



Unless molecular rearrangement has taken place the hydrocarbon obtained by Tiffeneau can, from its method of preparation, only be a mixture of (III) and (IX), and this may account for its somewhat different properties.

Semmler‡ has described a hydrocarbon, *cyclolinaloolene*, b.p. 165–167°, d^{17}_D 0.8112, n_D 1.4602, which he obtained by the cyclisation of linaloolene. Since linaloolene has been shown to be identical with dihydromyrcene,§ this cyclic hydrocarbon should be identical with *cyclodihydromyrcene*. It is remarkable that it should have been found to have a somewhat lower boiling-point.

Attention must also be directed to the experiments of Chapman,|| who has shown that the hydrocarbon *squalene* on distillation over sodium, undergoes decomposition, one of the products being a hydrocarbon closely related to, but apparently not identical with, *cyclodihydromyrcene*.

* Schimmel's Report, 1911, Oct. p. 130.

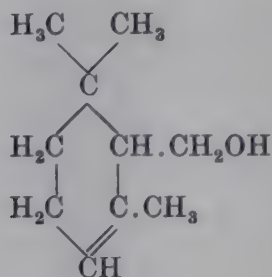
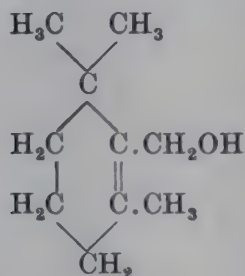
† Annalen, 1912, 387, 189.

‡ Ber. 1894, 27, 2521.

§ Schimmel's Report, 1911, Oct. p. 128.

|| J.C.S. 1918, 113, 464; 1923, 123, 777.

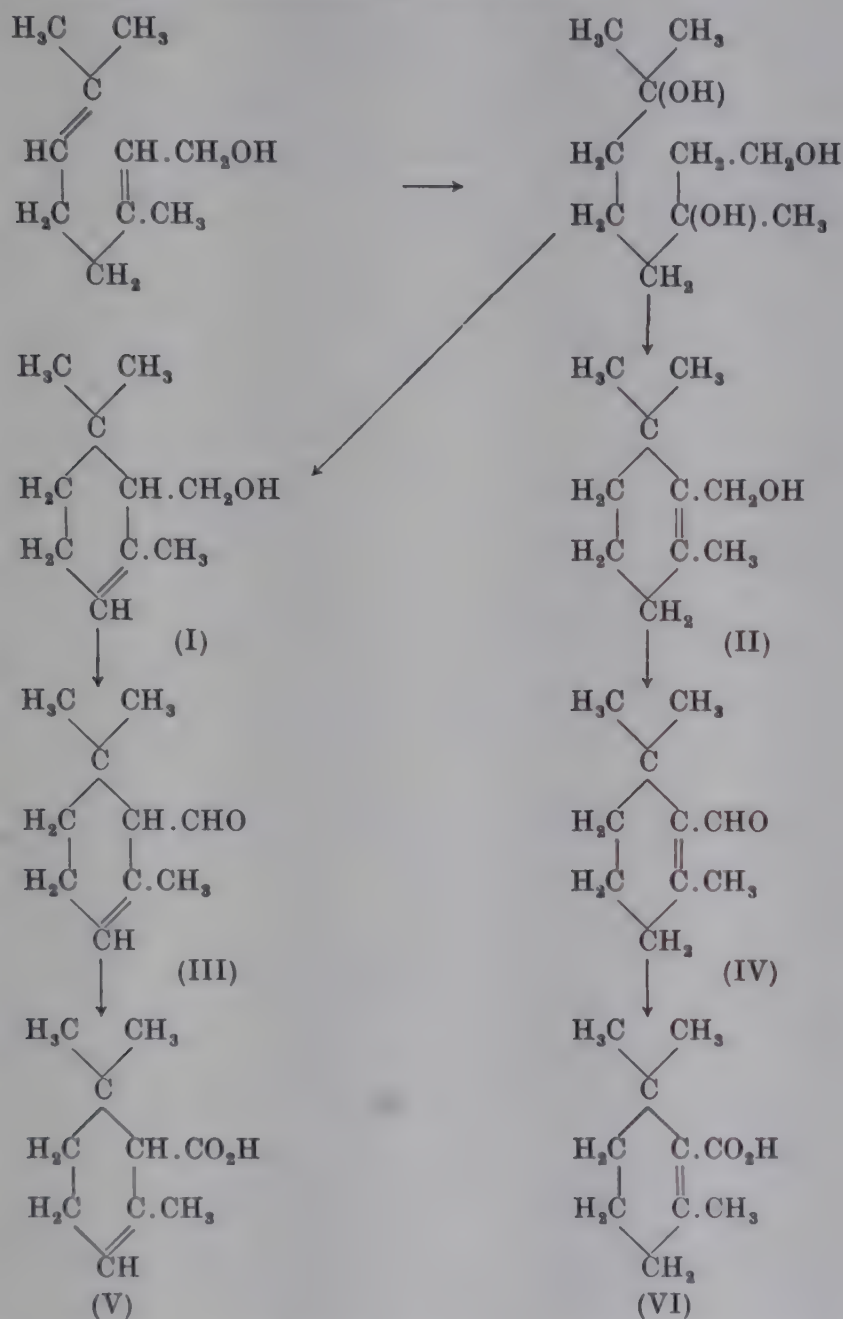
CYCLOGERANIOLS

 α -CYCLOGERANIOL(1:1:3-Trimethyl-2-methylol- Δ^3 -cyclohexene) β -CYCLOGERANIOL(1:1:3-Trimethyl-2-methylol- Δ^2 -cyclohexene)

The *cyclogeraniols* cannot be prepared directly from geraniol, since dehydration precedes cyclisation with consequent formation of cyclic hydrocarbons. It was, however, observed by Haarmann and Reimer* that, if the hydroxy group in geraniol was first protected by acetylation, then, by the action of either strong sulphuric acid or phosphoric acid, cyclisation could be effected with formation of *acetyl cyclogeraniol*. The *cyclogeraniol* obtained on hydrolysis was a mixture of α - and β -*cyclogeraniols*, (I) and (II), and had b.p. 95–100°/12 mm., d^{20}_D 0.935–0.955, n_D 1.48. The relative proportions of the α - and β -isomerides in the mixture are dependent upon the method adopted for ring closure. With sulphuric acid the β -derivative is mainly formed, the reverse being the case when phosphoric acid is used. The proportions of the isomerides present can be determined by oxidation with chromic acid, when a mixture of α - and β -*cyclo-citrals*, (III) and (IV), is obtained, and these on further oxidation

* G.P. 138141.

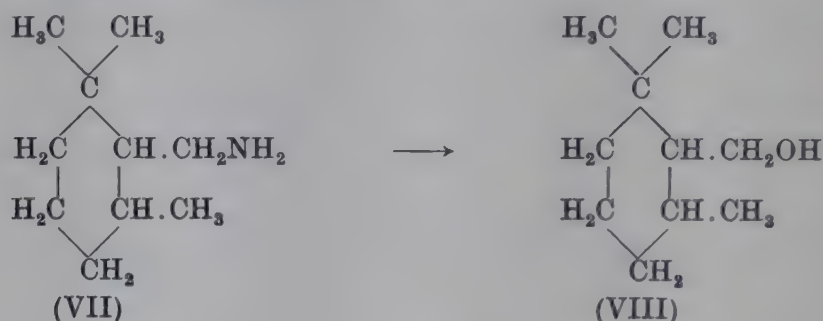
yield α - and β -cyclogeranic acids, (V) and (VI), the changes involved being represented by the scheme:



Pure β -cyclogeraniol does not appear to have been prepared, but, according to Bouveault,* the pure α -isomeride is formed when ethyl α -cyclogeranate (from α -cyclogeranic acid, m.p. 103.5°) is reduced with sodium and alcohol. It may be characterised by the preparation of the *phenylurethane*, which crystallises in needles, m.p. 75° .

* *Bull. Soc. chim.* 1910 [iv], 7, 354.

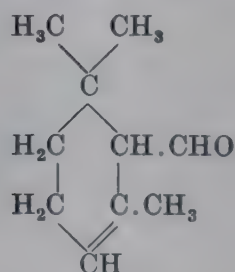
Hydrogenation of cyclogeranonitrile in the presence of Raney nickel gives *dihydrocyclogeranylamine* (VII),* which is converted by nitrous acid into a mixture of products, from which *dihydrocyclogeraniol* (cyclocitronellol) (VIII), b.p. $81^{\circ}/4$ mm., may be isolated. This substance (VIII) has also been prepared by cyclisation of citronellyl acetate,[†] and on oxidation with chromic acid it yields *dihydrocyclocitral* (p. 119).



CYCLOCITRALS

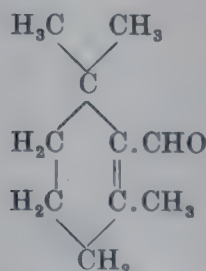
α -CYCLOCITRAL

(1:1:3-Trimethyl-2-formyl- Δ^3 -cyclohexene)



β -CYCLOCITRAL

(1:1:3-Trimethyl-2-formyl- Δ^2 -cyclohexene)



* Barbier, *Helv. Chim. Acta*, 1940, **23**, 524; Naves and Bachmann, *ibid.* 1943, **26**, 1334.

[†] Müller, *Ber.* 1921, **54**, 1466.

The most important cyclic derivatives of the aliphatic terpenes, other than the *p*-cymene derivatives, are the aldehydes α - and β -cyclocitral. They cannot be prepared by the direct cyclisation of either citral *a* or citral *b*, since these, on treatment with dehydrating agents, yield almost solely *p*-cymene.

The cyclocitrals were first obtained by Strebel* by the action of dilute sulphuric acid on either of the isomeric citrylidene-cyanoacetic acids (I) (p. 100), when α - and β -cyclocitrylidene-cyanoacetic acids (III) and (III a) are formed, the glycollic acid (II) being probably an intermediate product. These acids yield on hydrolysis with alkali a mixture of α - and β -cyclocitrals (IV) and (IV a) (see page 118).

Subsequent investigation showed that the mixture of cyclocitrals prepared by this method consisted mainly of β -cyclocitral. In the following year Haarmann and Reimer† found that when the condensation product of citral with aniline (or other primary amines) was treated with concentrated sulphuric acid and the product, after dilution, subjected to distillation in steam, a mixture of the cyclocitrals, in which the β -isomeride predominated, was obtained.

An interesting method for the preparation of the cyclocitrals from α - and β -cyclogeranic acids has been described by Merling.* By the series of reactions formulated below, the cyclogeranic acids (V) were converted into the diphenylamidines (VI), which on reduction with sodium and alcohol yielded the cyclocitrylidenedianilines (VII), these on hydrolysis with mineral acids giving the cyclocitrals (IV) and (IV a). Merling observed that both α - and β -cyclogeranic acids gave rise to mixtures of the cyclocitrals, a result in complete accord with the investigations of Thorpe and his collaborators on tautomerism. The method has been applied by Ruzicka and Schinz‡ for the preparation of 6-methylcyclocitral from 6-methylcyclogeranic acid.

As has been mentioned already (p. 114) the cyclocitrals can also be obtained by the oxidation of the cyclogeraniols.

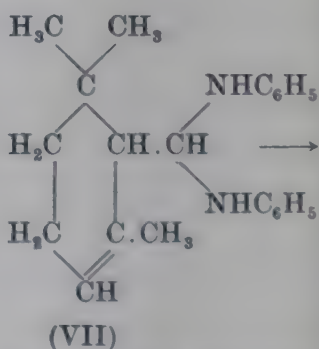
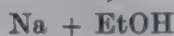
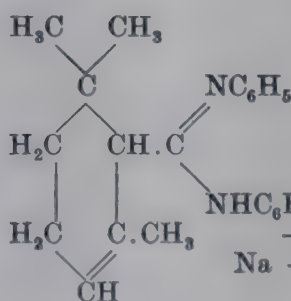
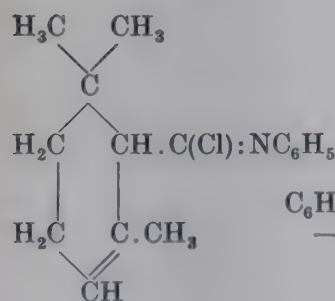
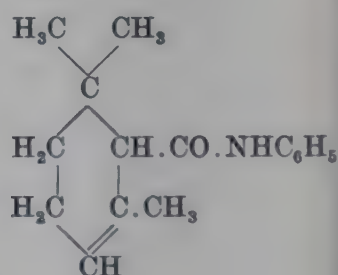
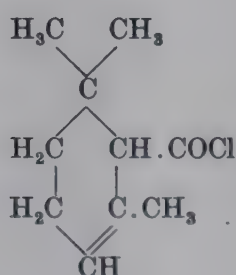
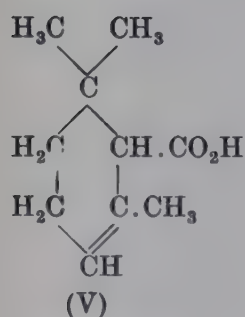
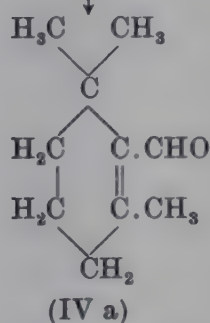
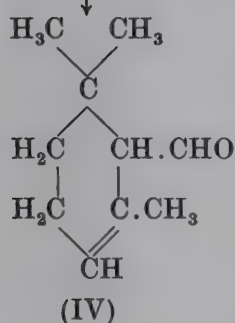
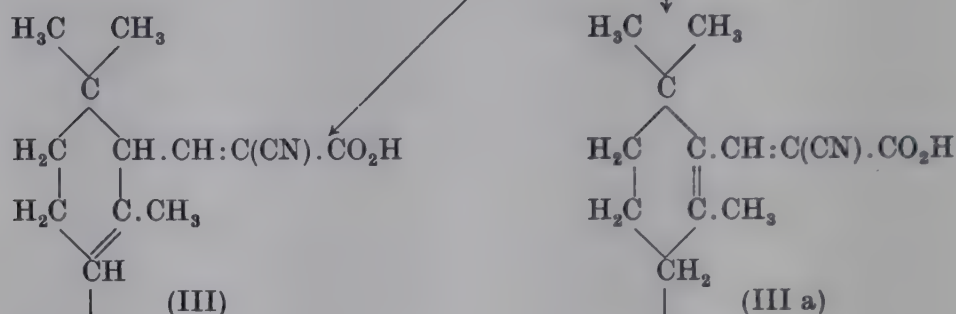
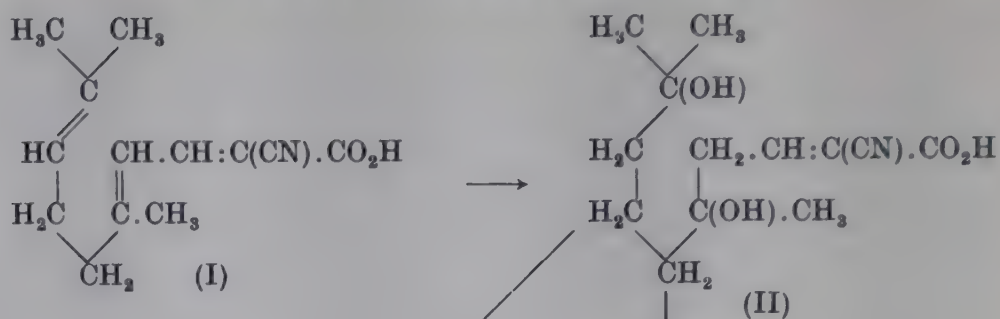
α -Cyclocitral may be separated most conveniently from its isomeride by treatment of the mixture with sodium amalgam in acetic acid solution, when β -cyclocitral is converted into high

* G.P. 108335; compare Tiemann, Ber. 1900, 33, 3719.

† G.P. 123747.

‡ Ber. 1908, 41, 2064.

§ Helv. Chim. Acta, 1940, 23, 959.

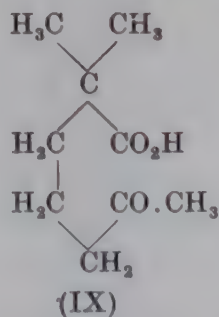
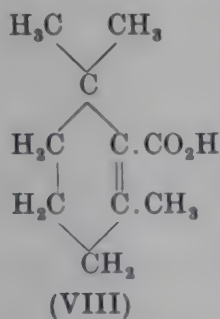


(For simplicity the reactions are shown for α -cyclogeranic acid as though proceeding without isomerisation at any stage.)

boiling derivatives, whereas the α -aldehyde is not attacked. Purified in this manner α -cyclocitral has b.p. $90-95^\circ/20$ mm., d^{15}_D 0.925. It may be characterised by the preparation of the semicarbazone, m.p. 206° , the 2:4-dinitrophenylhydrazone, m.p. $171-172^\circ$, and by oxidation to α -cyclogeranic acid, m.p. 103.5° . It can be condensed with acetone to yield α -ionone, but it is less reactive than the β -aldehyde.

For the separation of β -cyclocitral from α -cyclocitral advantage is taken of the observation of Haarmann and Reimer* that, when a mixture of the semicarbazones of the aldehydes is distilled in steam in the presence of phthalic acid, only the semicarbazone of the β -aldehyde is hydrolysed, that of the α -aldehyde being unattacked. β -Cyclocitral is an oil with an odour reminiscent of that of carvone, b.p. $112-114^\circ/29$ mm., $d^{15.25}_D$ 0.9566, $n^{13.3}_D$ 1.4970.† The oxime‡ crystallises well and has m.p. 84° ; the semicarbazone§ separates from ethyl acetate in leaflets, m.p. $166-167^\circ$.

On oxidation with potassium permanganate in alkaline solution, β -cyclocitral gives β -cyclogeranic acid (VIII) and geric acid (IX), thus establishing the position of the ethylenic linkage.



Reduction of β -cyclocitral with hydrogen in the presence of colloidal palladium yields dihydrocyclocitral (X)^{||} which on oxidation with silver oxide gives dihydrocyclogeranic acid (XI), m.p. 82° , identical with that obtained by catalytic hydrogenation of cyclogeranic acid.[†]

* G.P. 139957.

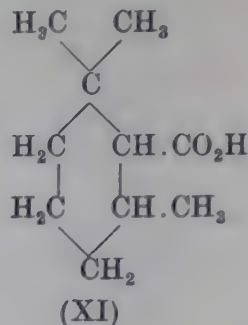
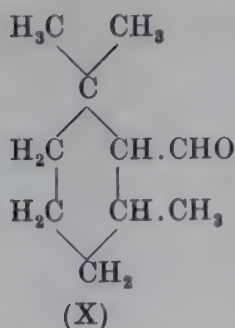
† Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], 82, 120.

‡ Alessandri, *Atti R. Accad. Lincei*, 1910 [v], 19, II, 122.

§ Tiemann, *Ber.* 1900, 33, 3721. Alessandri (*loc. cit.*) states that the semicarbazone has m.p. 209° . This divergent result would appear to require confirmation, since it is possible that the latter separated the semicarbazone of α -cyclocitral, which has m.p. 204° .

^{||} Skita, *Ber.* 1909, 42, 1635.

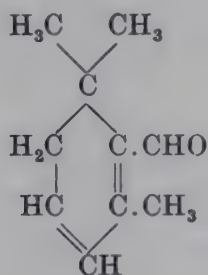
¶ Barbier, *Helv. Chim. Acta*, 1940, 23, 524; compare Wallach, *Annalen*, 1919, 418, 56.



β -cyclocitral condenses very readily with acetone to yield β -ionone.

SAFRANAL

(1:1:3-Trimethyl-2-formyl- $\Delta^{2:4}$ -cyclohexadiene)



Although it has been frequently suggested that terpene derivatives might occur in nature as glucosides, direct evidence of this was first supplied by Kuhn and Winterstein* by their investigation of the chemistry of picrocrocin, the bitter principle of saffron (from *Crocus sativus*). Picrocrocin, $\text{C}_{16}\text{H}_{26}\text{O}_7$, m.p. 156° , first isolated by Kayser† and later investigated by Winterstein and Teleczky‡ was shown by Kayser to be a glucoside, whilst Winterstein and Teleczky observed that the aglucone had the composition $\text{C}_{10}\text{H}_{14}\text{O}$ and contained a carbonyl group. It remained, however, for Kuhn and Winterstein to elucidate fully the structures of picrocrocin and its *aglucone*, safranal.

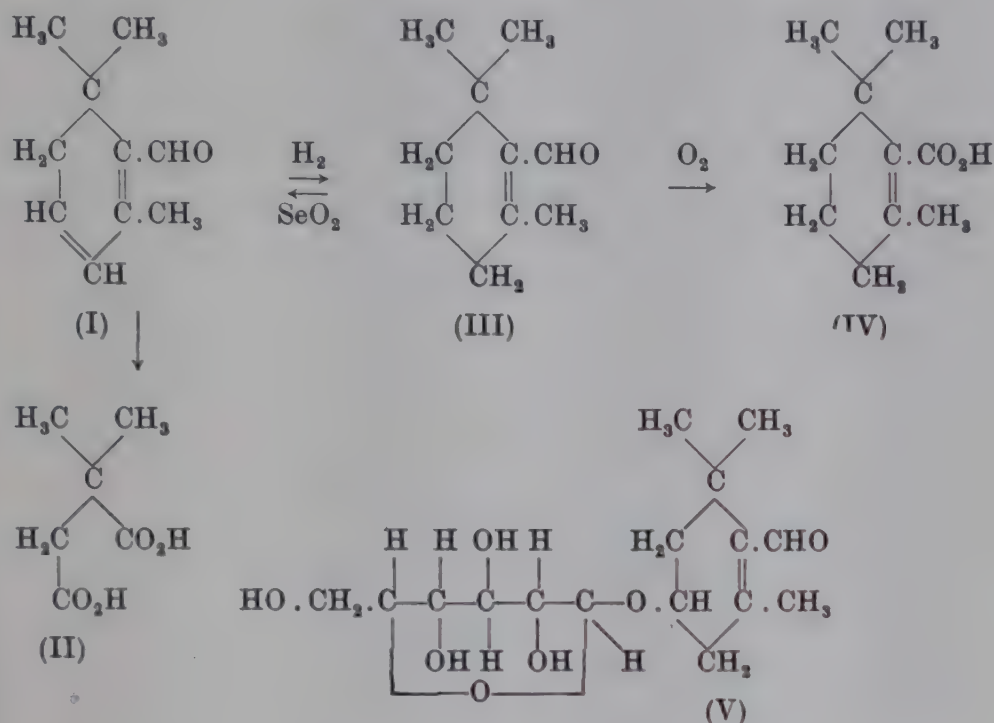
Picrocrocin on hydrolysis with either acid or alkali yields glucose and safranal, the hydrolysis proceeding without the addition of water. Safranal was readily shown to be the aldehyde (I). It gave on oxidation with potassium permanganate *as*-dimethylsuccinic acid (II) and on partial hydrogenation

* Ber. 1934, 67, 344.

† Ibid. 1884, 17, 2228.

‡ Helv. Chim. Acta, 1922, 5, 376; Z. physiol. Chem. 1922, 120, 141.

β -cyclocitral (III) identified by comparison with the synthetic aldehyde (semicarbazone, m.p. 163–165°) and by oxidation to β -cyclogeranic acid (IV). The structure assigned to safranal has been confirmed by Kuhn and Wendt's synthesis,* who prepared



it by the oxidation of β -cyclocitral with selenium dioxide. For picrocrocin Kuhn and Winterstein suggest (V); the addition of *d*-glucose to safranal must be in the 4:5-position, since the absorption spectrum of the glucoside shows that the ethylenic linkage is in the α : β -position to the aldehyde group.

Safranal is an oil, b.p. 70°/1 mm. (bath temperature), d_4^{19} 0.9730, n_D^{19} 1.5281, *oxime*, m.p. 65°, *semicarbazone*, m.p. 175°, *thiosemicarbazone*, m.p. 199–200°, 2:4-*dinitrophenylhydrazones*, m.p. 186°. As mentioned above, on catalytic hydrogenation in the presence of platinum oxide it yields β -cyclocitral, whilst with a silica-platinum catalyst three molecules of hydrogen are absorbed. Attempts to oxidise it to the corresponding acid, *safranin acid*, have been unsuccessful, but the acid, m.p. 63°, *p*-bromophenacyl ester, m.p. 102°, has been synthesised by Wendt.†

* *Ber.* 1936, **69**, 1549.

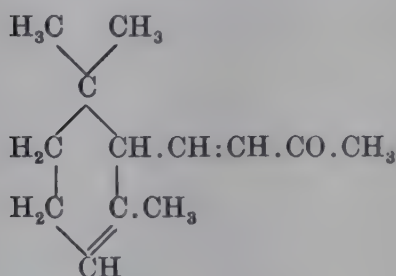
† *Ibid.* 1941, **74**, 1242.

Kuhn and Winterstein* have discussed the possible phytochemical relationship of picrocrocin and crocin, whilst Kuhn, Moewus and Wendt† have shown that both picrocrocin and safranal have a sex-determinative action for certain green algae, a property not shown by safranic acid.

THE IONONES

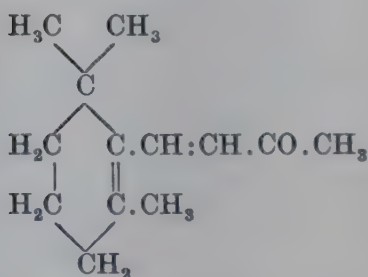
α -IONONE

(α -Cyclocitrylideneacetone)



β -IONONE

(β -Cyclocitrylideneacetone)



Penfold and Phillip‡ have shown that β -ionone is present in the essential oil obtained from *Boronia megastigma* Nees. A mixture of the *ionones* was, however, first prepared by Tiemann and Krüger§ by treating *pseudoionone* with a mixture of dilute sulphuric acid and glycerol. In subsequent years, owing to their great technical importance, a variety of methods for the cyclisation of the aliphatic ketone have been devised, amongst

* *Loc. cit.*

† *Ber.* 1939, 72, 1702.

‡ *J. Roy. Soc. W. Australia*, 1928, 14, 1; compare Sabetay, *Bull. Soc. chim.* 1929 [iv], 45, 1169.

§ *Ber.* 1893, 26, 2693.

the reagents used being sodium bisulphate, dilute nitric acid, concentrated sulphuric acid and phosphoric acid. These methods are in the main described in the patent literature, but Hibbert and Cannon* have given detailed methods for their laboratory preparation. In most cases a mixture of α - and β -ionones is obtained, their relative proportions being dependent upon the reagent used for the cyclisation. With sulphuric acid† the main product is β -ionone, whilst with phosphoric acid or formic acid α -ionone is chiefly obtained.‡ The mixture of ionones obtained in this manner has somewhat varying properties, depending upon the actual composition of the mixture, but the following may be regarded as average values: b.p. 126–128°/12 mm., d_{10}^{15} 0.9350–0.9403, n_D^{20} 1.5033–1.5051. Cyclisation of *pseudo*-ionone semicarbazone with phosphoric acid gives almost pure β -ionone.§

The ionones can be most readily freed from other impurities by conversion into the compound which they yield on treatment with a boiling solution of sodium bisulphite.|| Any neutral products are removed by means of ether and the bisulphite compound decomposed with alkali and distilled in steam. Unchanged *pseudo*ionone is removed by treatment with an alcoholic solution of potassium hydroxide.

Ionone has an odour reminiscent of cedar wood, but in very dilute alcoholic solution it resembles that of violets. It is largely manufactured for use in the synthetic perfume industry.

The separation of the α - and β -ionones was first carried out by Tiemann¶ by taking advantage of the difference in the solubility of their *semicarbazones*. β -Ionone semicarbazone is very sparingly soluble and can thus be obtained pure; the crude α -ionone semicarbazone, remaining in the mother liquor, was reconverted into the ketone by hydrolysis and the *oxime* prepared, when, on cooling to a low temperature, α -iononeoxime crystallised, that of β -ionone being an oil. Regeneration of β -ionone from its semicarbazone is preferably accomplished with

* *J. Amer. C.S.* 1924, **46**, 119.

† Tiemann, *Ber.* 1898, **31**, 870.

‡ Chuit and Naef, *B.P.* 18333; Haarmann and Reimer, *G.P.* 133563. For a recent study of the effects of different acids, see Royals, *Ind. Eng. Chem.* 1946, **38**, 546.

§ Heilbron, Jones and Spinks, *J.C.S.* 1939, p. 1554.

|| Tiemann, *Ber.* 1898, **31**, 851, 1737.

¶ *Ibid.* pp. 874, 1737.

dilute sulphuric acid, since the older method, involving distillation with steam in the presence of phthalic anhydride, leads to partial isomerisation.*

The difference in properties of the sodium bisulphite derivatives of the isomerides may also be utilised for their separation. It was shown by Haarmann and Reimer[†] that, when the mixed sodium bisulphite compound is distilled in steam, that formed from β -ionone was decomposed, the β -ionone distilling with the steam; from the residue α -ionone could be obtained by treatment with alkali. A somewhat different method was adopted by Chuit and Naef.[‡] They precipitated the sodium bisulphite compound of α -ionone, which they formulated $C_{13}H_{21}OSO_3Na, 3H_2O$, by saturating the solution with sodium chloride, the β -ionone compound $C_{13}H_{21}OSO_3Na, 2H_2O$, remaining in solution. The two isomerides were then regenerated by treatment with alkali and distillation in steam.

Pure α - and β -ionones can also be obtained, as previously mentioned (pp. 119, 120), by condensation of α - and β -cyclocitrals with acetone.

α -Ionone is a colourless oil with a somewhat sweeter odour than the β -isomeride and resembling more closely that of violets. The physical constants of the ketone have been very carefully determined by Auwers and Eisenlohr:[§] (from the oxime) b.p. $123-124^\circ/11$ mm., d^{20}_D 0.932, n^{20}_D 1.4980; (from the bisulphite compound) b.p. $127.6^\circ/12$ mm., d^{20}_D 0.9287, n^{20}_D 1.5002. It is most readily characterised by the preparation of the oxime, m.p. $89-90^\circ$, which crystallises from a strongly cooled solution in light petroleum. The semicarbazone has m.p. $142-143^\circ$, the phenylsemicarbazone m.p. 187° , the p-bromophenylhydrazone m.p. $142-143^\circ$, and the 2:4-dinitrophenylhydrazone m.p. 151° .

The constitution of α -ionone (I) was determined by Tiemann^{||} by an investigation of the products formed on oxidation with potassium permanganate. The primary product of the oxidation was the ketonic acid (II), which could not be isolated since it

* Young, Cristol, Andrews and Lindenbaum, *J. Amer. C.S.* 1944, **66**, 855; see also Heilbron, Johnson, Jones and Spinks, *J.C.S.* 1942, p. 727.

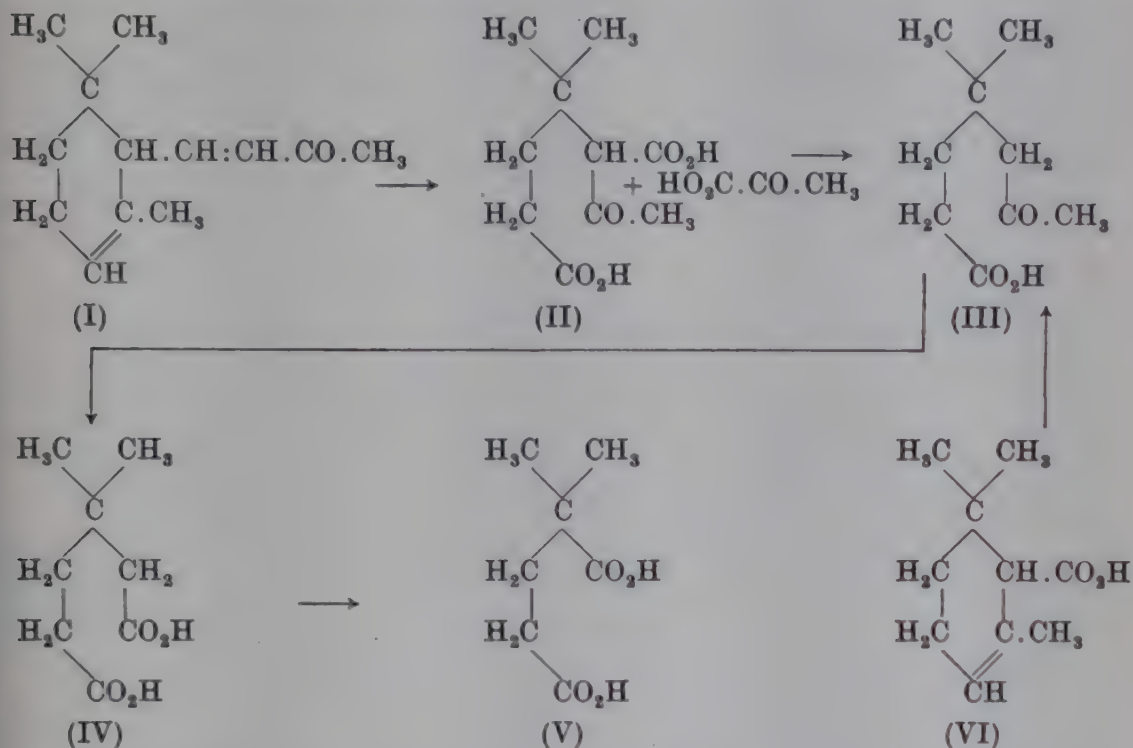
† G.P. 106512; compare Naves and Bachmann, *Helv. Chim. Acta*, 1943, **26**, 2151.

‡ B.P. 18333.

§ *J. pr. Chem.* 1910 [ii], **82**, 126.

|| *Ber.* 1900, **33**, 3726.

immediately lost carbon dioxide with formation of *isogeronic acid* (III). Other products of the oxidation were $\beta\beta$ -dimethyladipic acid (IV) and $\alpha\alpha$ -dimethylglutaric acid (V). The reactions involved are represented by the scheme:



The constitution of *isogeronic acid* (III), which is an oil (*semicarbazone*, m.p. 198°), was further proved by its oxidation with sodium hypobromite solution to $\beta\beta$ -dimethyladipic acid (IV). It may be mentioned that *isogeronic acid* is also obtained when α -cyclogeranic acid (VI), m.p. 103.5° , prepared from geranic acid by the action of concentrated sulphuric acid, is oxidised with potassium permanganate.*

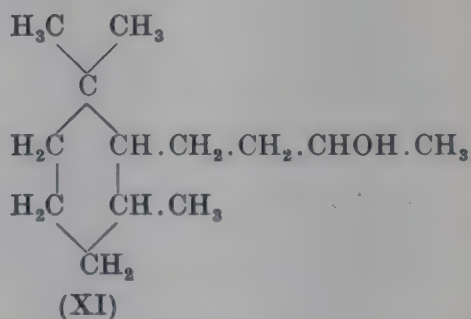
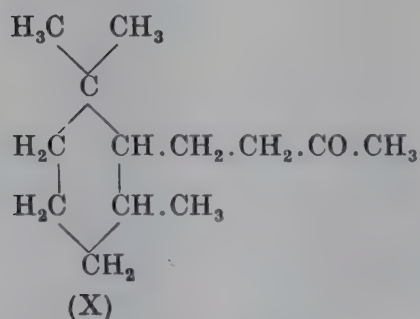
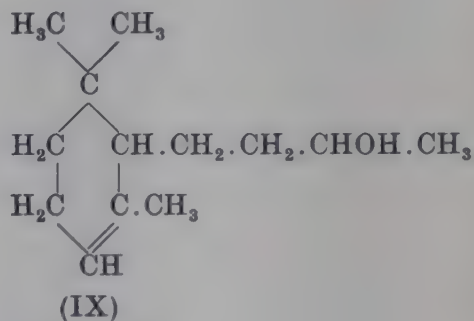
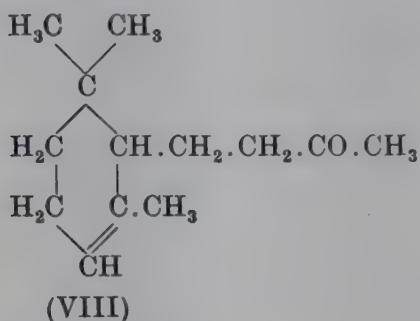
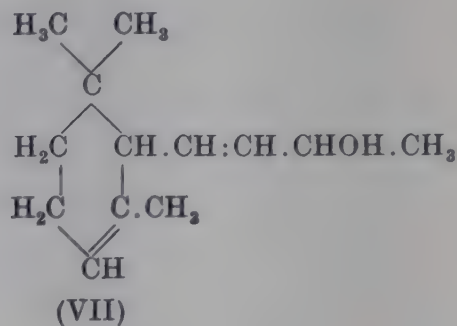
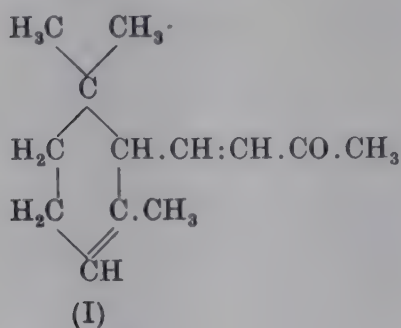
Numerous products may be obtained by the reduction of α -ionone under various conditions. With aluminium isopropoxide it yields α -ionol (VII), b.p. $127^\circ/14$ mm.[†] On catalytic hydrogenation[‡] α -ionone gives, according to conditions, one or more of the following products: *dihydro- α -ionone* (VIII), b.p.

* Tiemann and Semmler, *Ber.* 1893, **26**, 2725; compare Bouveault, *Bull. Soc. chim.* 1910 [iv], **7**, 350.

† Palfray, Sabetay and Kandel, *Compt. rend.* 1936, **203**, 1376; see also Kandel, *Ann. Chim.* 1939, **11**, 73.

‡ Skita, *Ber.* 1912, **45**, 3312; Ruzicka, *Helv. Chim. Acta*, 1919, **2**, 352; Ruzicka and Fischer, *ibid.* 1934, **17**, 633; Naves and Bachmann, *ibid.* 1943, **26**, 2151; 1944, **27**, 626; Palfray *et al.*, *loc. cit.*

121–122°/14 mm.; *dihydro- α -ionol* (IX), b.p. 131°/14 mm.; *tetrahydroionone* (X), b.p. 126–127°/14 mm.; *tetrahydroionol* (XI), b.p. 134°/15 mm.



Dihydro- α -ionone (VIII) may also be obtained by reduction of α -ionone with sodium and alcohol* or by ketonic hydrolysis of *cyclogeranylacetoacetic ester*.† The position of the ethylenic linkage in the dihydro-derivatives (VIII) and (IX) is proved by the fact that β -ionone, on reduction under similar conditions, yields products which are isomeric with, but not the same as, (VIII) and (IX).

α -Ionone on treatment with hydriodic acid and red phosphorus has been shown by Tiemann and Krüger‡ to yield a bicyclic hydrocarbon, *ionene*. This hydrocarbon was exhaustively studied by its discoverers and also by Baeyer,§ and was originally

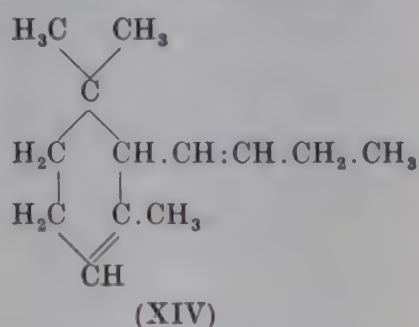
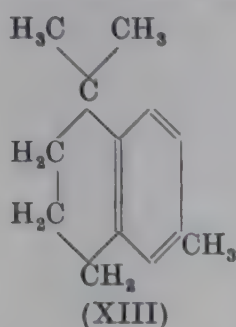
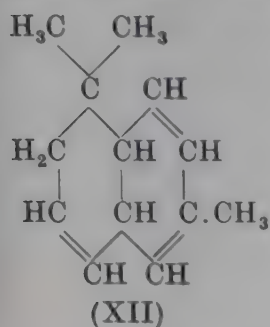
* Naves and Bachmann, *loc. cit.*

† *Ber.* 1893, 26, 2693.

† Ruzicka and Fischer, *loc. cit.*

§ *Ibid.* 1899, 32, 2438.

formulated as (XII). Bogert and Fourman,* however, have shown that ionene is a true benzenoid hydrocarbon, of structure (XIII), and this conclusion has been confirmed by synthesis.†



By the distillation of α -iononehydrazone with potassium hydroxide, Kishner‡ has shown that the unsaturated hydrocarbon α -ionane (XIV) is formed.

The resolution of α -ionone has been accomplished by fractional crystallisation of the menthylhydrazones.§ The *d*- α -ionone showed $[\alpha]_D^{23} + 347^\circ$, and the *l*- α -ionone $[\alpha]_D^{27} - 406^\circ$, the latter being rather more pure than the former. A number of derivatives of each form were also prepared.

β -Ionone, the methods for the preparation of which have been discussed above, has according to Auwers and Eisenlohr|| the constants: (from semicarbazone) b.p. $140^\circ/18$ mm., $d^{17}_4 0.946$, $n^{17}_D 1.521$; (from the sodium bisulphite compound) b.p. $140^\circ/16$ mm., $d^{15}_4 0.9488$, $n^{16}_D 1.520$. The oil has a distinctive odour resembling cedar wood, but in alcoholic solution it has a strong odour of violets. It can be characterised by the preparation of the semicarbazone, m.p. $148-149^\circ$, and the *p*-bromophenylhydrazone, m.p. $116-118^\circ$.

As in the case of α -ionone, Tiemann¶ established the constitution of β -ionone (XV) by an examination of the products formed on oxidation with potassium permanganate. The degradation resulted in the formation of hydroxyionolactone (XVI), geronic acid (XVII), $\alpha\alpha$ -dimethyladipic acid (XVIII), $\alpha\alpha$ -dimethylglutaric acid (XIX) and *as*-dimethylsuccinic acid (XX).

* *J. Amer. C.S.* 1933, **55**, 4670.

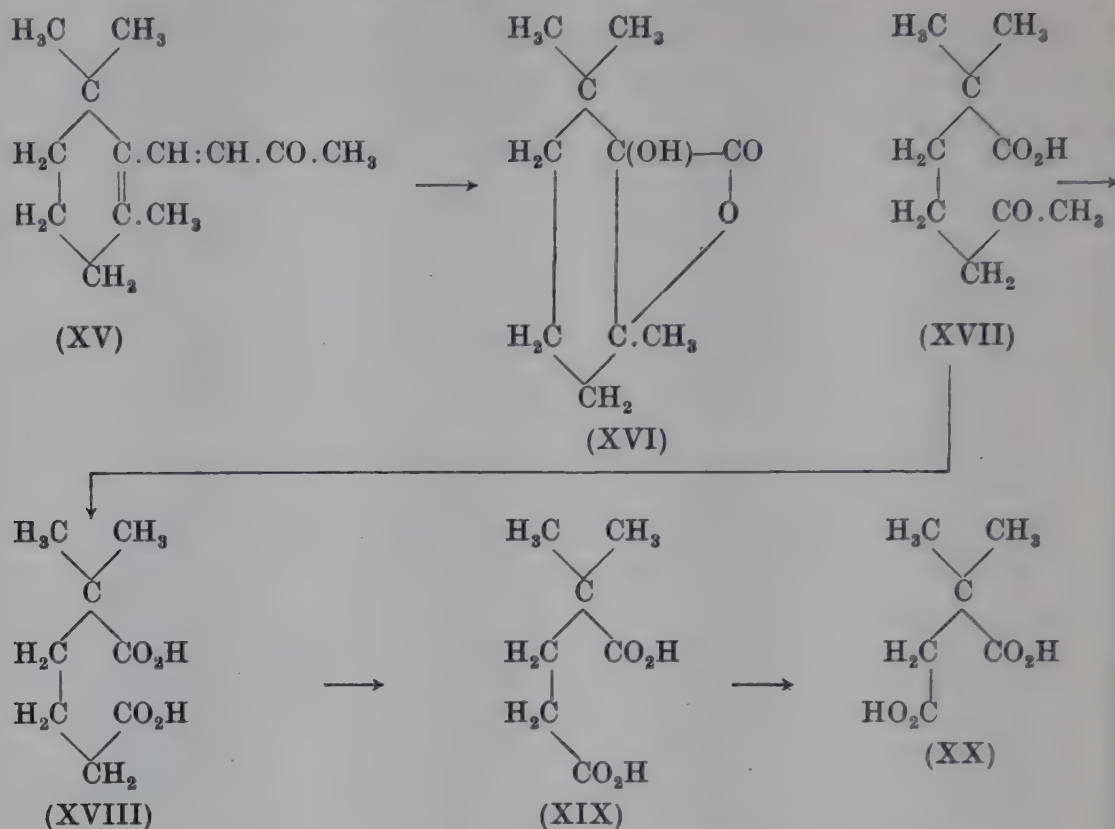
† Bogert, Davidson and Apfelbaum, *ibid.* 1934, **56**, 959.

‡ *J. Russ. Phys. Chem. Soc.* 1911, **43**, 1398.

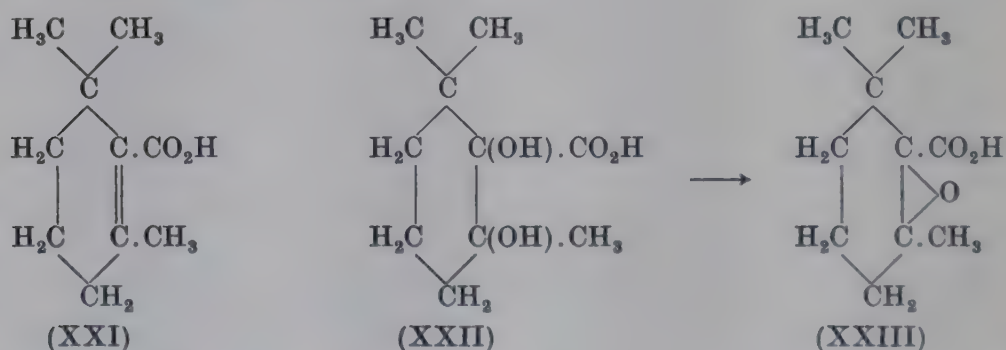
§ Sobotka, Bloch, Cahnmann, Feldbau and Rosen, *J. Amer. C.S.* 1943, **65**, 2061.

|| *J. pr. Chem.* 1911 [ii], **84**, 68; compare Heilbron, Johnson, Jones and Spinks, *J.C.S.* 1942, p. 727.

¶ *Ber.* 1898, **31**, 857; 1900, **33**, 3703.



The constitution of *geronic acid*, an oil (*semicarbazone*, m.p. 164°),* was confirmed by its oxidation with sodium hypobromite to $\alpha\alpha$ -dimethyladipic acid.



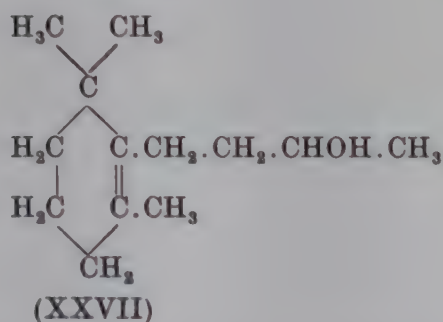
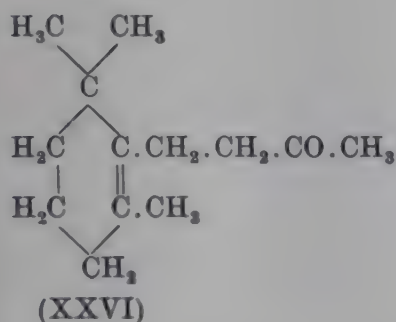
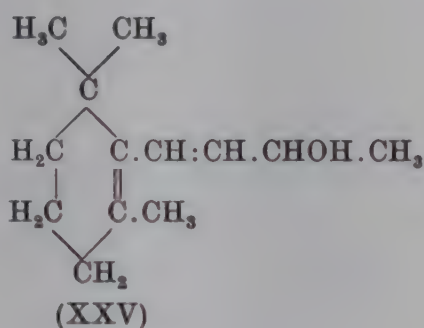
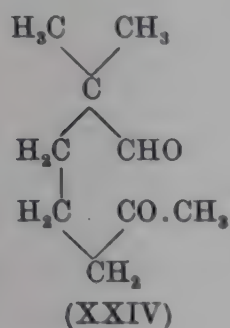
It is not without interest to note that contrary to expectation β -cyclogeranic acid (XXI), m.p. $93-94^\circ$, does not yield geronic acid on oxidation. The primary product of the oxidation, the *glycollic acid* (XXII), passes apparently into the *oxide* (XXIII), which on further oxidation yields $\alpha\alpha$ -dimethylglutaric acid (XIX).

With ozone, β -ionone gives *geronaldehyde* (XXIV), together with some of the above products.†

* Compare Rupe and Liechtenhan, *Ber.* 1908, **41**, 1284.

† Pummerer, Rebmann and Reindel, *Ber.* 1931, **64**, 492; 1933, **66**, 798.

The reduction products from β -ionone are very similar to those derived from α -ionone (p. 125) and have been studied by the workers already mentioned in that connection. With hydriodic acid and red phosphorus it yields ionene (XIII), and, with aluminium isopropoxide, β -ionol (XXV), b.p. $130^{\circ}/14$ mm., is obtained. On hydrogenation under various conditions it gives dihydro- β -ionone (XXVI), b.p. $127^{\circ}/15$ mm., dihydro- β -ionol (XXVII), m.p. 39.5° , b.p. $132^{\circ}/14$ mm., tetrahydroionone (X), and tetrahydroionol (XI).



It is beyond the scope of the present work to describe the many reactions in which β -ionone has been employed, but attention must be drawn to its importance as a possible starting material for the synthesis of vitamin A and other polyenes, an account of which has been given by Jones.*

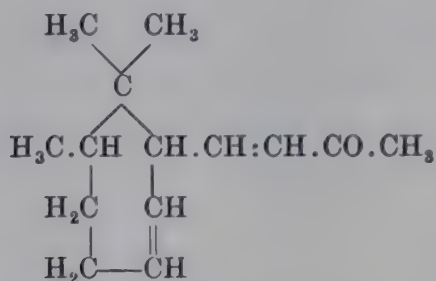
The structures assigned to the α - and β -ionones are supported by the absorption spectra of the ketones.† The Raman spectra have been studied by Naves and Bachmann.‡

* *Ann. Reports*, 1941, **38**, 180; see also Lindenbaum, Andrews and Young, *J. Amer. C.S.* 1944, **66**, 2130; Sobotka, Darby, Glick and Bloch, *ibid.* 1945, **67**, 403; Andrews, Cristol, Lindenbaum and Young, *ibid.* p. 715.

† Ruzicka, Seidel and Firmenich, *Helv. Chim. Acta*, 1941, **24**, 1434; Burawoy, *J.C.S.* 1941, p. 20; Young, Cristol, Andrews and Lindenbaum, *J. Amer. C.S.* 1944, **66**, 855.

‡ *Helv. Chim. Acta*, 1944, **27**, 97.

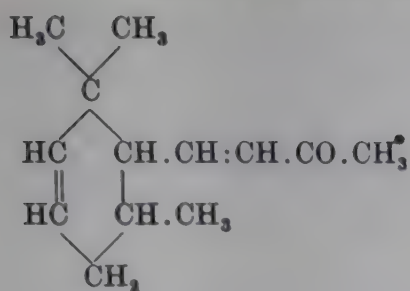
IRONE

(2- $[\Delta^{\alpha\beta}$ - γ -Ketobutenyl]-1:1:7-trimethyl- Δ^3 -cycloheptene)

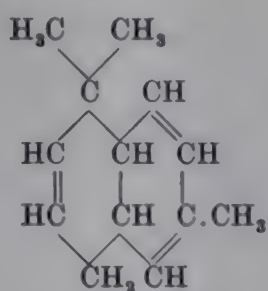
The ketone, irone, $\text{C}_{14}\text{H}_{22}\text{O}$, occurs in the oil present in orris root (*Iris florentina*, *germanica* and *pallida*) and possibly also in that from cassia flowers (*Acacia Farnesiana*). Irone was first isolated and studied by Tiemann and Krüger,* an investigation involving great experimental difficulties since only 1 gramme of the ketone was obtained from 15 kilos of the orris root. From an analysis of the ketone, purified either through its oxime or phenylhydrazone, Tiemann and Krüger concluded that it had the composition, $\text{C}_{13}\text{H}_{20}\text{O}$, and although this and the structure which they assigned to the ketone has now been shown to be incorrect, it would appear desirable to give an outline of this work in view of the fact that it led directly to the preparation of the ionones (p. 122), the chemistry of which later proved to be of such great importance in the elucidation of the structure of vitamin A.

The formula (I) suggested by Tiemann and Krüger was based essentially on the following considerations. On treatment with hydriodic acid and red phosphorus it was converted with loss of water into a hydrocarbon, *irene* (II), which gave on oxidation with chromic acid the *lactone* (IV), *dehydroirene* (III) being an unstable intermediate product. Oxidation of the lactone with potassium permanganate yielded *ireginene dicarboxylic acid* (V), which on further oxidation gave the *keto-tribasic acid* (VI) and finally the *tribasic acid* (VII). Distillation of the ammonium salt of (VII) gave the *imide* (VIII) from which, by elimination of carbon dioxide, *dimethylhomophthalimide* (IX) was obtained.

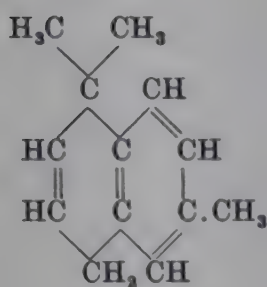
* Ber. 1893, 26, 2675; 1895, 28, 1757; 1898, 31, 809.



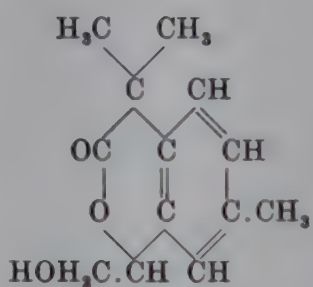
(I)



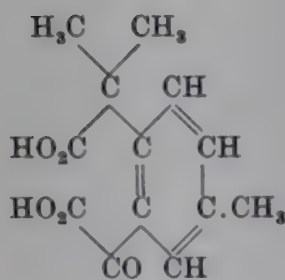
(II)



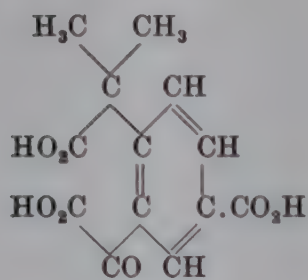
(III)



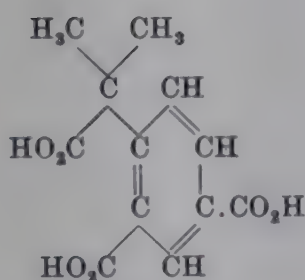
(IV)



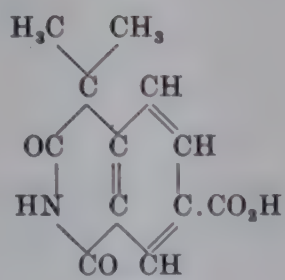
(V)



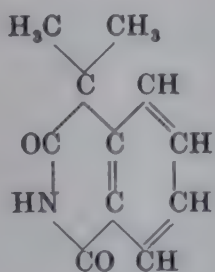
(VI)



(VII)



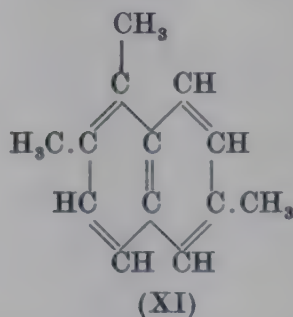
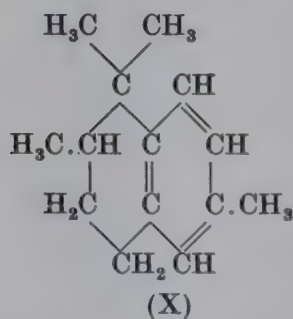
(VIII)



(IX)

This formula for irone appeared at the time to receive support from the observation that the acids (VI), (VII), (VIII) and (IX) were obtained by the degradation of ionene (p. 126) and also from a synthesis of the ketone reported by Merling and Welde.* This synthetic "irone" was later shown by Ruzicka and Brugger† to be α -ionone.

The first doubt of the correctness of Tiemann and Krüger's formula arose when Ruzicka‡ observed that tetrahydroirone and tetrahydroionone, prepared by the catalytic hydrogenation of the unsaturated ketones, showed a marked difference in their physical properties, a difference difficult to explain on stereochemical grounds. An explanation of this divergence was given some years later when Ruzicka, Seidel and Schinz§ showed that irone had the composition $C_{14}H_{22}O$, and irene, $C_{14}H_{20}$. For this hydrocarbon, b.p. 119–123°/10 mm., d_4^{20} 0.935, n_D^{20} 1.521, they suggested the structure (X) since it gave on dehydrogenation with selenium 1:2:6-trimethylnaphthalene (XI). This formula for irene was confirmed by Bogert and Apfelbaum's synthesis.|| For



irone itself Ruzicka and his collaborators¶ have advanced the structure represented by (XII). The ketone contains two ethylenic linkages, since it yields on catalytic hydrogenation tetrahydroirone and the absorption spectrum shows that one of these linkages must be in the $\alpha\beta$ -position to the carbonyl group.** The three main products obtained by ozonolysis, followed by oxida-

* Ber. 1908, **41**, 2066; *Annalen*, 1909, **366**, 129.

† *J. pr. Chem.* 1941 [ii], **158**, 125.

‡ *Ibid.* 1933, **16**, 1143.

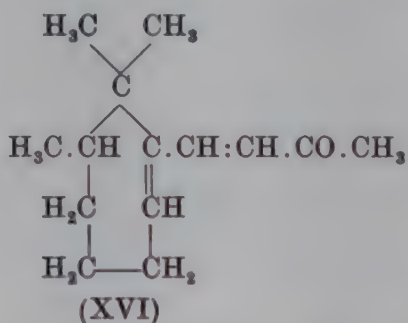
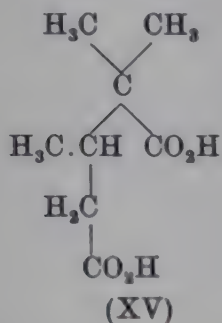
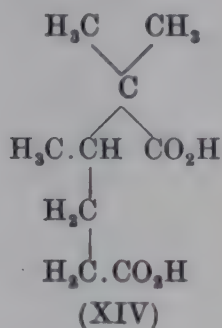
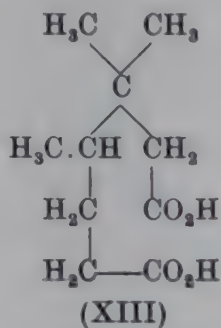
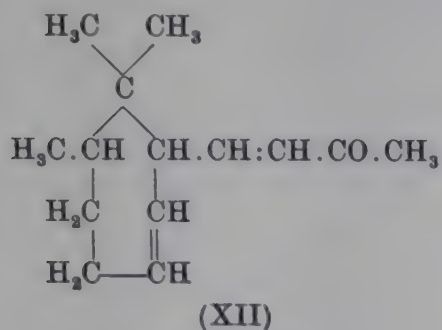
* *Helv. Chim. Acta*, 1919, **2**, 352.

|| *J. Amer. C.S.* 1938, **60**, 930.

¶ Ruzicka, Schinz and Seidel, *Helv. Chim. Acta*, 1940, **23**, 935; Ruzicka, Seidel and Firmenich, *ibid.* 1941, **24**, 1434; Ruzicka, Seidel, Schinz and Pfeiffer, *ibid.* 1942, **25**, 188.

** Ruzicka, Seidel and Firmenich, *loc. cit.*; Gillam and West, *Nature*, 1941 **148**, 114; *J.C.S.* 1942, pp. 95, 483.

tion with chromic acid, were *d*- $\beta\beta\gamma$ -trimethylpimelic acid (XIII), *d*- $\alpha\alpha\beta$ -trimethyladipic acid (XIV) and *dl*- $\alpha\alpha\beta$ -trimethylglutaric acid (XV).



Whilst these experiments leave little doubt that the main ketonic fraction of orris root oil is essentially represented by (XII), as Ruzicka and his collaborators and also Gillam and West have pointed out, other ketones are present in the oil in varying proportions, dependent upon the source of the oil.

Irone is a liquid which in dilute alcoholic solution possesses the characteristic odour of violets. Somewhat varying constants have been recorded for the pure ketone, and although it shows some tendency to isomerise on digestion with dilute sulphuric acid, conversion to the ketone (XVI), which might be anticipated, does not appear to occur. Ruzicka, Seidel and Schinz* have found that irone can be separated most conveniently from orris root oil by means of its phenylhydrazone *p*-sulphonic acid, according to the method devised by Schmidt,† the ketone regenerated from the hydrazone being further purified through its crystalline *phenylsemicarbazone*, m.p. 177–178°; a second *phenylsemicarbazone*, m.p. 155–160°, has been described. For irone separated from the former, Ruzicka, Seidel and Firmenich‡ give the constants: b.p. 89°/0.5 mm., $d_4^{21^\circ}$ 0.9353, $n_D^{21^\circ}$ 1.5001,

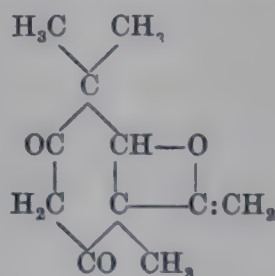
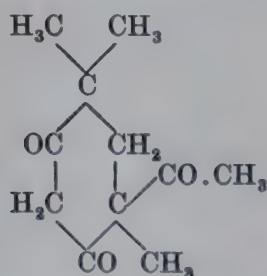
* *Loc. cit.*† *Z. angew. Chem.* 1900, 13, 189.‡ *Loc. cit.*

$\alpha_D + 60^\circ$; $[\alpha]_D + 70^\circ$ (in alcohol). Gillam and West* for a specimen of the ketone purified through its phenylhydrazone *p*-sulphonic acid have recorded the values, b.p. $106-108^\circ/2$ mm., $d_{15}^{20^\circ} 0.912$, $n_D^{17^\circ} 1.5017$, $\alpha_D + 37.5^\circ$, another specimen of the ketone having b.p. $116-118^\circ/3$ mm., $d_{15}^{25^\circ} 0.915$, $n_D^{21^\circ} 1.5015$, $\alpha_D 46.6^\circ$. Irone is most readily identified by the preparation of its *p*-bromophenylhydrazone, m.p. 175° ; the semicarbazone is difficult to purify and it melts indefinitely at $190-195^\circ$. The thiosemicarbazone is also a somewhat unsatisfactory derivative and divergent results have been recorded. According to Ruzicka, Seidel and Schinz† it has m.p. $110-112^\circ$, whilst Chuit‡ gives m.p. 185° ; Gillam and West§ prepared two thiosemicarbazones melting respectively at 180° and $107-115^\circ$. The oxime has m.p. 121.5° .

As mentioned above, irone on catalytic hydrogenation yields tetrahydroirone, b.p. $135-136^\circ/10$ mm., $d_4^{15^\circ} 0.925$, $n_D^{25^\circ} 1.4731$, $\alpha_D + 35.5^\circ$, semicarbazone, m.p. 203° , *p*-nitrophenylhydrazone, m.p. $138-139^\circ$, 2:4-dinitrophenylhydrazone, m.p. $113-114^\circ$.

ANGUSTIONE AND DEHYDROANGUSTIONE

(4-Acetyl-2:2:4-trimethylcyclohexane-1:5-dione and
Dehydro-4-acetyl-2:2:4-trimethylcyclohexane-1:5-dione)



In 1923 Penfold^{||} isolated from the essential oil present in the leaves and terminal branchlets of *Backhousia angustifolia*, which grows in Queensland, a substance possessing phenolic properties to which he provisionally assigned the formula, $C_{10}H_{14}O_3$. The same phenol was found also in small quantity in the oils from

* *Loc. cit.*

† *Loc. cit.*

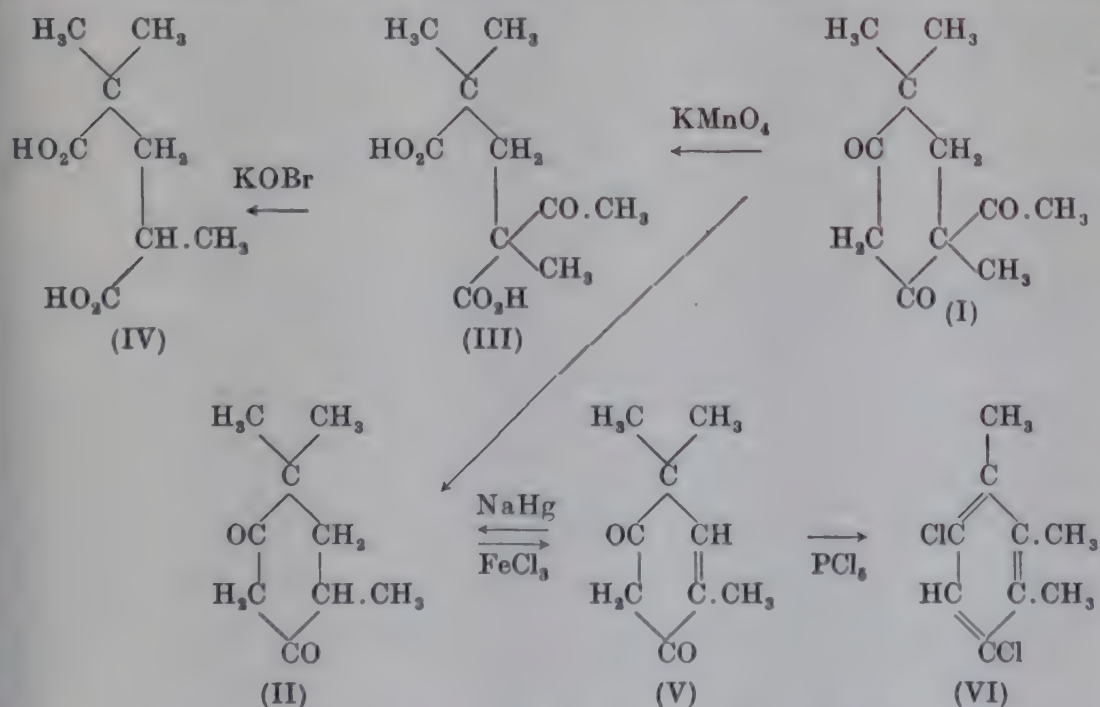
‡ *Rev. gén. Chimie*, 1903, 6, 473.

§ *Loc. cit.*

^{||} *J. Proc. Roy. Soc. New South Wales*, 1923, 57, 300.

Boronia thujina, var. A,* and *Eucalyptus Rariflora*.† Subsequent investigations by Gibson, Penfold and Simonsen,‡ and by Cahn, Gibson, Penfold and Simonsen,§ showed the phenol to be a mixture of two β -diketones, *angustione* and *dehydroangustione*, having the compositions $C_{11}H_{16}O_3$ and $C_{11}H_{14}O_3$ respectively. The two liquid ketones, which occur in the essential oils in varying proportions, can best be separated by conversion into their crystalline *amino*-compounds from which they can be regenerated by the action of dilute aqueous sodium hydroxide.

l-Angustione, b.p. $129^\circ/15$ mm., d_{20}^{20} 1.089, n_D^{20} 1.5092, $[\alpha]_{5461} -5.56^\circ$, is a colourless, somewhat viscid oil, with a faint unpleasant odour, its alcoholic solution giving with ferric chloride an intense orange-red colour. The structure (I) for angustione was established by its fission on treatment with aqueous potassium hydroxide at 150° into 1:1:3-*trimethylcyclohexane-4:6-dione* (II), m.p. $130-131^\circ$, and acetic acid, the constitution of the former being proved by its oxidation with potassium hypobromite to $\alpha\alpha\gamma$ -*trimethylglutaric acid* (IV). The laevorotatory form of this acid was obtained when angustione was oxidised with potassium hypobromite or with potassium permanganate



* Penfold, *J. Proc. Roy. Soc. New South Wales*, 1929, **62**, 231.

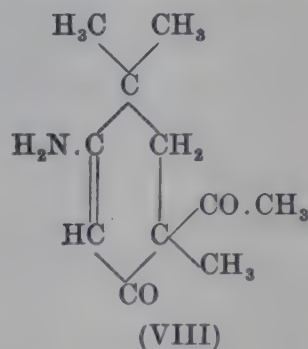
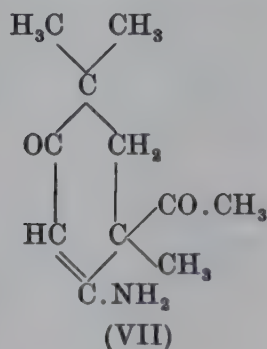
† Penfold, Radcliffe and Short, *ibid.* 1930, **64**, 101.

‡ *J.C.S.* 1930, p. 1184.

§ *Ibid.* 1931, p. 286.

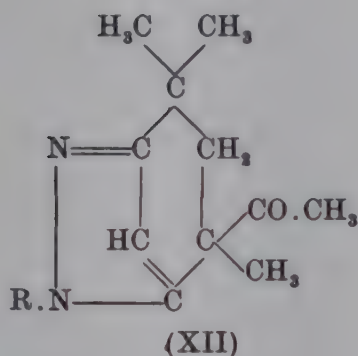
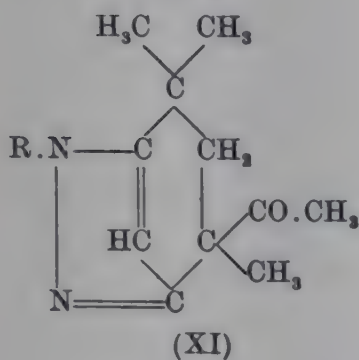
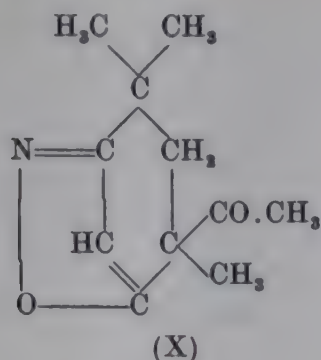
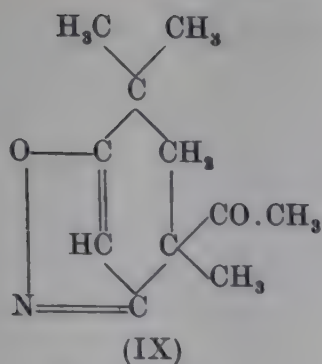
in acetone, the primary product of the latter reaction, probably the keto-acid (III), being oxidised with potassium hypobromite to (IV). On digestion of angustione with ferric chloride in dilute acetic acid 1:1:3-*trimethyl- Δ^2 -cyclohexene-4:6-dione* (V), m.p. 159–160°, was formed, yielding on oxidation with potassium permanganate dimethylmalonic acid, and on reduction with sodium amalgam the saturated ketone (II). The primary product of the oxidation of angustione is the saturated dione (II), since this is oxidised by ferric chloride to (V). Confirmation of the structures assigned to (II) and (V) was obtained by their conversion by phosphorus pentachloride into 1:2:3-*trimethyl-4:6-dichlorobenzene* (VI).

Aminoangustione, prepared by the action of concentrated ammonia on the diketone, crystallised from *cyclohexane* in massive prisms, m.p. 130–131°, $[\alpha]_{5461} - 8.6^\circ$ (in alcohol). Aminoangustione is probably represented by either (VII) or (VIII). A further characteristic derivative of angustione is the

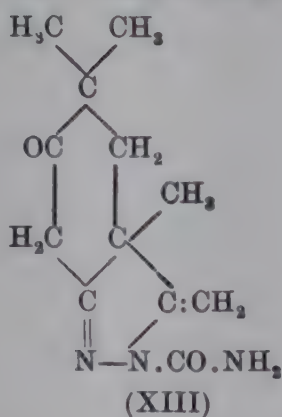


copper salt, $C_{22}H_{30}O_6Cu$, crystallising from benzene in blue prisms, m.p. 192–193°, which can also be used for its purification.

Although angustione reacts readily with the usual carbonyl reagents the derivatives have not a simple structure. With hydroxylamine an *anhydro-oxime*, $C_{11}H_{15}O_2N$, m.p. 41–43°, was obtained, probably either (IX) or (X). By the action of phenylhydrazine or of *p*-bromophenylhydrazine, products of probably analogous structures (XI) and (XII), m.p. 119–120° and 191°, respectively, were obtained. With semicarbazide an *anhydro-semicarbazone*, m.p. 145° (decomp.), was obtained which was soluble in alkali and gave with ferric chloride an intense indigo blue coloration. This substance was probably represented by (XIII), the potential enolic form accounting for these properties.

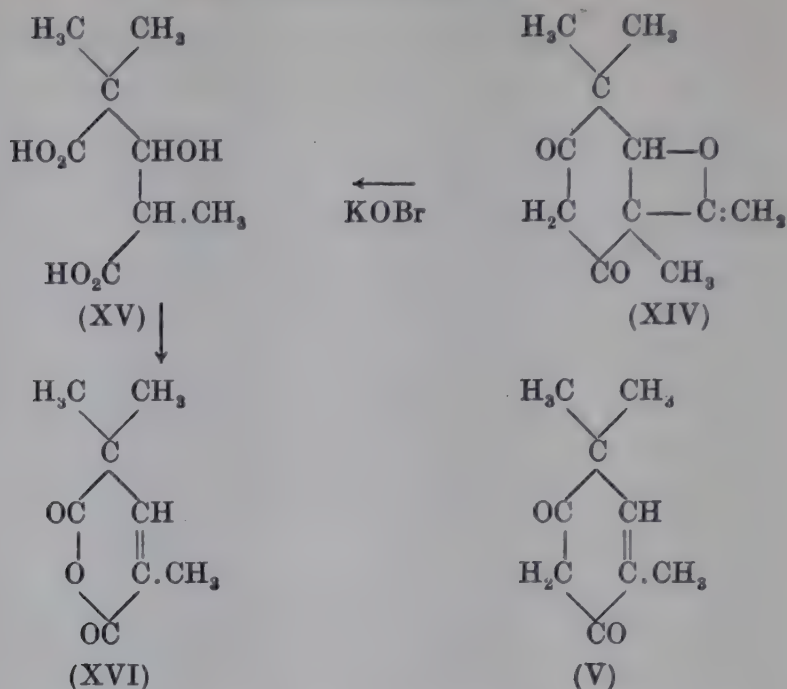


(R = C₆H₅ or BrC₆H₄)



1-Dehydroangustione (XIV), b.p. 126–127°/11 mm., d_{20}^{20} 1.103, n_D^{20} 1.5313, $[\alpha]_D -2.03^\circ$, is, like angustione, an oil and closely resembles it in its properties. It is most readily purified through its *amino*-derivative, m.p. 151°. On oxidation with potassium hypobromite in alkaline solution it yields *trans*- β -hydroxy- $\alpha\alpha$ -trimethylglutaric acid (XV) and its dehydration product, the *anhydride* of *cis*- $\alpha\alpha$ -trimethylglutaconic acid (XVI).

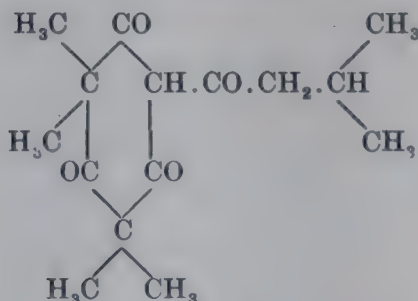
Additional proof of the structure (XIV) assigned to the dione was furnished by its conversion by either alkali or dilute sulphuric acid into 1:1:3-trimethyl- Δ^2 -cyclohexene-4:6-dione (V). On catalytic hydrogenation *l*-dehydroangustione gave *dl*-angustione, b.p. 127°/14 mm., d_{20}^{20} 1.082, n_D^{20} 1.5087, *amino*-derivative, m.p.



138–140°, *copper salt*, m.p. 203–204°, *anhydro-oxime*, m.p. 57–58°. With carbonyl reagents dehydroangustione reacts in a similar manner to angustione. Two forms of the *anhydrosemicarbazone* have been described, the α -form, m.p. 138–139°, and the β -, m.p. 173–175°. The *anhydro-p-bromophenylhydrazone* had m.p. 247–248°, whilst the *anhydro-oxime*, which was dextrorotatory, $[\alpha]_{5461} + 4.95^\circ$ (in alcohol) had m.p. 79–80°.

LEPTOSPERMONE

(4-iso Valeryl-2:2:6:6-tetramethylcyclohexane-1:3:5-trione)

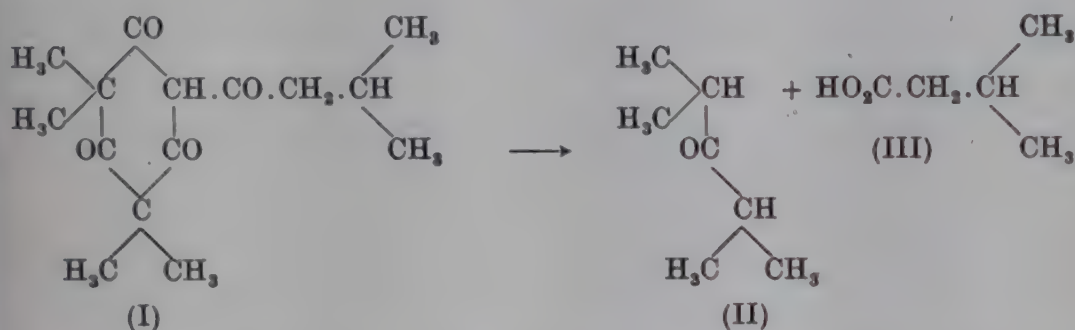


During an investigation of the essential oil from *Leptospermum flavescens*, which grows in New South Wales, Penfold* separated a substance showing phenolic properties to which he gave the

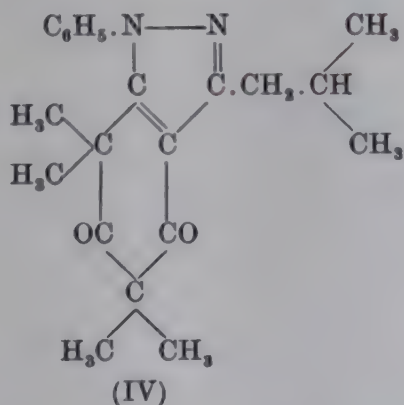
* *J. Proc. Roy. Soc. New South Wales*, 1920, **54**, 199; 1921, **55**, 51.

name *leptospermol* and to which he provisionally assigned the formula $C_{14}H_{20}O_4$. The same substance was isolated later from the essential oils of *L. ericoides** and from *L. scoparium*.† Although Gardner suggested that leptospermol was a monobasic acid, a careful re-examination by Briggs, Penfold and Short‡ has shown it to be a β -diketone and to have the composition $C_{15}H_{22}O_4$. In accordance with this finding they have changed the name to *leptospermone*.

They suggest that leptospermone has the structure (I), since it gives on oxidation with potassium permanganate *diisopropyl ketone* (II) and *isovaleric acid* (III).



Although rigid proof of this structure has not so far been obtained, support is afforded by the facts that on oxidation with nitric acid it yields dimethylmalonic acid, and on hydrolysis with hydrochloric acid it gives tetramethylphloroglucinol.‡



* Johnson and Short, *Rep. Aust. Assoc. Sci.* 1923, **16**, 222; Short, *J.S.C.I.* 1926, **46**, 96 T.

† Inder, Thesis, Univ. of New Zealand, 1923; Short, *loc. cit.*; Gardner, *J.S.C.I.* 1924, **43**, 34 T; 1925, **44**, 528 T.

‡ *J.C.S.* 1938, p. 1193.

§ Briggs, Hassal and Short, *J.C.S.* 1945, p. 706.

Attention may be directed to the fact that the structure assigned to leptospermone cannot be built up from three isoprene units.

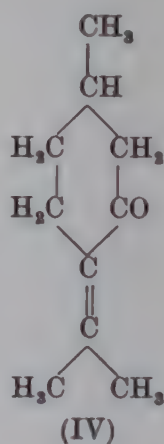
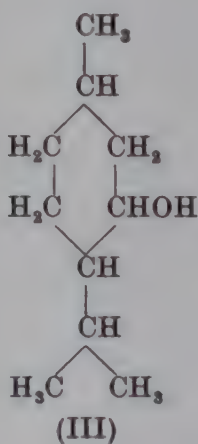
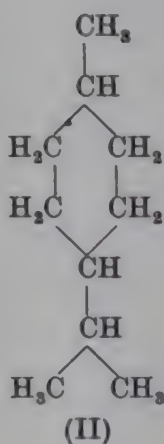
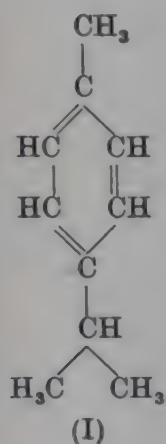
Leptospermone, b.p. $146^{\circ}/10$ mm., $d_4^{19.5^{\circ}}$ 1.0688, $n_D^{19.5^{\circ}}$ 1.500, is a faintly yellow oil having a somewhat unpleasant odour. It is optically inactive and its alcoholic solution gives with ferric chloride an intense orange-red coloration. It can best be characterised by the preparation of its *anilino*-derivative, m.p. 91° , and its *anhydrophenylhydrazone* (IV), m.p. 118° .

PART II

THE MONOCYCLIC TERPENES AND THEIR DERIVATIVES

INTRODUCTION

As was mentioned previously (p. 4), the monocyclic terpenes may be regarded as derivatives of *p*-cymene (I) or the corresponding hydrogenated hydrocarbon, 1-methyl-4-isopropylcyclohexane (II), for which the name *p*-menthane was suggested by Wagner.*

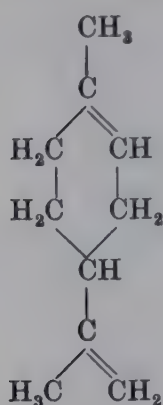


Although neither the saturated hydrocarbon nor any of the isomeric menthenes, $C_{10}H_{18}$, are plant products, many derivatives, such as menthol (III) or pulegone (IV), occur in nature. All the natural hydrocarbons are “dihydro-*p*-cymenes” (*p*-menthadienes), $C_{10}H_{16}$, of which there are theoretically fourteen possible isomerides. Of these only six—(V), (VI), (VIII), (IX), (X), (XI)—have been shown to be natural products, although it is not improbable that β -terpinene (VII) is always present in natural α -terpinene. Other isomerides have been prepared by W. H. Perkin, jun., and his collaborators (compare footnote, p. 150).

Although the cyclic hydrocarbons are more stable than the corresponding acyclic substances, they oxidise very readily and

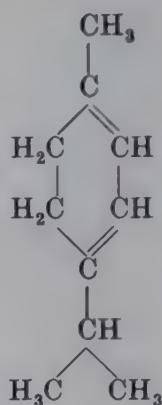
* Ber. 1894, 27, 1636, footnote.

tend to isomerise and polymerise, especially when distilled at atmospheric pressure. It is very doubtful if any of the natural hydrocarbons have been prepared in a state of purity.

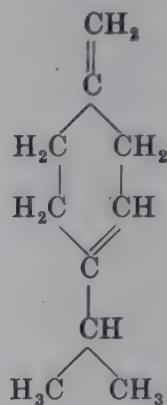


(V)

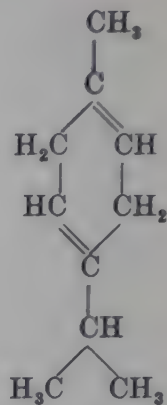
Limonene



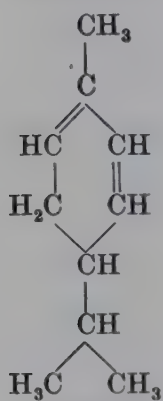
(VI)

 α -Terpinene

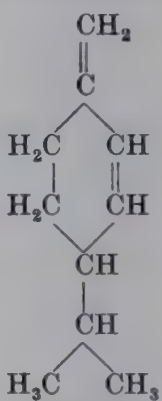
(VII)

 β -Terpinene

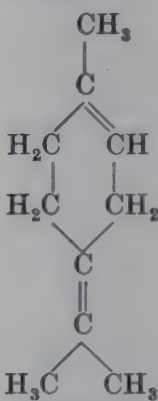
(VIII)

 γ -Terpinene

(IX)

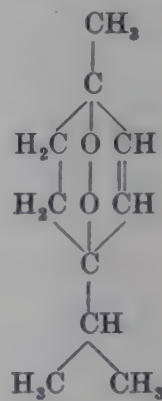
 α -Phellandrene

(X)

 β -Phellandrene

(XI)

Terpinolene



(XII)

Ascaridole

The study of chemistry of the cyclic terpene alcohols and ketones has raised many interesting stereochemical problems, which will be considered later. Special mention may be made of the remarkable peroxide, ascaridole (XII) (p. 446). This is the only naturally occurring peroxide and the determination of its precursor and of the part which it plays in the plant economy would be of peculiar interest.

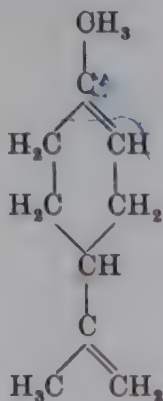
CHAPTER I

HYDROCARBONS

LIMONENE

(*dl*-LIMONENE = DIPENTENE)

($\Delta^{1:8(9)}$ -*p*-Menthadiene or 1-Methyl-4-isopropenyl- Δ^1 -cyclohexene)



With the possible exception of α -pinene, no terpenes occur more widely distributed in nature, or have played a more fundamental part in the development of terpene chemistry, than the hydrocarbons *d*- and *l*-limonene and the *dl*- (racemic) form which is known as *dipentene*.

Limonene forms the main constituent of the terpene fraction of a number of oils, amongst which may be mentioned the oils of lemon, orange, caraway, dill and bergamot.*

In view of its wide distribution in nature, and the facility with which it may be prepared from other terpenes, it is not remarkable that the chemistry of limonene has formed the subject of numerous investigations. It lies beyond the scope of this work to discuss in detail the historical development of the chemistry of the terpenes and only the salient facts germane to the elucidation of the constitution of limonene will be discussed in the sequel.

Prior to 1870, both *d*- and *l*-limonene and dipentene had been prepared in a fairly pure state and recognised as hydrocarbons of the formula $C_{10}H_{16}$, differing in constitution from that present

* Compare Gildemeister and Hoffmann, *Die Ätherischen Öle*, 3rd ed., I.

in oil of turpentine (pinene). It was also known that, on treatment with hydrogen chloride, a *dihydrochloride*, $C_{10}H_{16}, 2HCl$, could be prepared which melted at about 50° . In 1872 an observation of great importance was made by Oppenheim,* who discovered that both the hydrocarbon from oil of turpentine, and that from lemon oil (citrene)[†] could be converted into cymene by treatment with bromine followed by elimination of hydrogen bromide. This would not, however, appear to have been the first recognition that the terpenes were hydrogenated derivatives of cymene, since Greville Williams[‡] had already obtained cymene from turpentine by the action of bromine and sodium.

A few years later Tilden[§] showed that limonene gave with nitrosyl chloride a characteristic crystalline additive compound, a *nitrosochloride*, from which a nitroso-body was produced by the action of alkali. Making use of these new derivatives Tilden, partly in collaboration with Shenstone, now divided the terpenes into two classes: (1) the turpentine group, b.p. $156-160^{\circ}$, *nitroso-derivative*, m.p. 129° , (2) the orange group, b.p. $174-176^{\circ}$, *nitroso-derivative*, m.p. 71° . He recognised further that sylvestrene did not belong to either of these classes.

Tilden's discovery of the terpene nitrosochlorides was of fundamental importance to terpene chemistry, and it must rank in the same category with Fischer's introduction of phenylhydrazine as a reagent for the sugars. It now became possible to identify the terpenes present in the various essential oils and so to commence a study of their constitution.

The next landmark in the study of the terpenes was the preparation by Wallach^{||} of *d-limonene tetrabromide*, m.p. $104-105^{\circ}$, and *dipentene tetrabromide*, m.p. 125° . Wallach had found that dipentene, a name which he suggested for the optically inactive hydrocarbon variously known as di-isoprene, carvene, etc., gave a tetrabromide identical with that slowly formed by the action of bromine on cineole, whilst citrene gave a lower melting tetrabromide, which, although it resembled that from

* *Ber.* 1872, 5, 628; 1873, 6, 456, 915.

[†] Limonene has been known by a number of names of which the following are the more important: hesperidene, citrene, carvene, cinene, di-isoprene, isoterbenthene, cautchene.

[‡] *Proc. Roy. Soc.* 1860, 10, 517.

[§] *J.C.S.* 1877, 31, 554.

^{||} *Annalen*, 1884, 225, 304, 318.

dipentene in many ways, was not identical with it. It was not until some years later,* after the discovery of *l*-limonene, that dipentene was recognised to be the *dl*- (racemic) form of limonene, and it may be mentioned that this recognition was delayed by the fact that dipentene had been given an incorrect boiling-point. With nitrosochlorides, nitroso-derivatives and tetrabromides available for their characterisation, the identification and the classification of the terpenes advanced rapidly.

It was early recognised that limonene was closely related to terpin, α -terpineol and carvone, and the elucidation of its constitution resulted from a determination of the structure of these substances. Flavitzky† found that when either *d*- or *l*- α -pinene was treated with an alcoholic solution of sulphuric acid, an alcohol, $C_{10}H_{17}OH$ (α -terpineol) was formed, which on dehydration gave a terpene, b.p. 179° , d^{20}_{D} 0.848 , which was optically active ($[\alpha]_D$ 57.6° and -61°) in the same sense as the pinene from which it had been prepared. This hydrocarbon was recognised by Flavitzky as identical with the hydrocarbon, limonene, present in lemon oil. At about the same time Tilden‡ and Wallach§ had observed that the glycol, *terpin*, could be converted into α -terpineol by the action of dilute acids, and, also, that this alcohol on dehydration gave limonene. It was known from previous investigations that terpin, α -terpineol, limonene and dipentene all gave the same dihydrochloride.

The close relationship of limonene and carvone was shown by the investigations of Goldschmidt and Zürrer,|| who proved carvoxime to be identical with the nitrosolimonene prepared by Tilden and Shenstone¶ by the action of alkali on limonene nitrosochloride. A correlation of these results became possible by the further experimental researches of Baeyer and Wallach and by the theoretic insight of Wagner.

Although the terpenes had been formulated as derivatives of a partially reduced cymene by Oppenheim, there was no definite evidence as to whether they contained an *n*-propyl or an *iso*-propyl group, the latter being, however, regarded as the more probable. This view was supported by the general acceptance of

* *Annalen*, 1888, **246**, 221.

† *Ber.* 1879, **12**, 1022, 1406, 2354; 1887, **20**, 1956.

‡ *J.C.S.* 1879, **35**, 287.

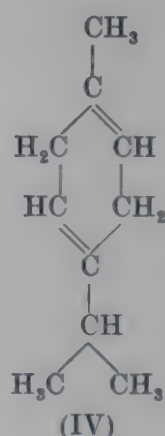
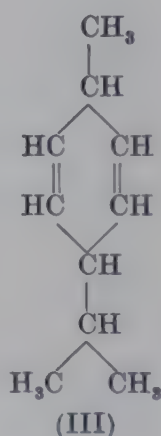
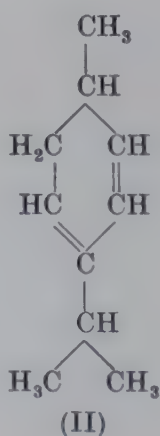
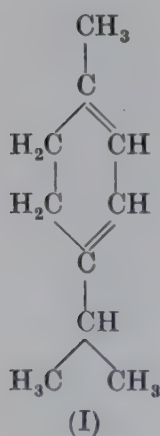
|| *Ber.* 1885, **18**, 2220.

§ *Annalen*, 1885, **230**, 258.

¶ *J.C.S.* 1877, **31**, 554.

a dicyclic structure for pinene and camphor and by Brühl's* researches on the molecular refraction of the terpenes, which indicated the presence of two ethylenic linkages in limonene and one in pinene. It remained, however, for Widman† to prove that the terpenes were derivatives of *p*-cymene.

In 1885 Goldschmidt‡ suggested that limonene was represented by (I), although he recognised that it was improbable, since it did not contain an asymmetric carbon atom, and two years later he replaced it by (II). This formula was accepted by Wallach,§ who, however, at that time considered dipentene to have a different structure (III). Shortly afterwards Brühl,|| on the basis of the work referred to above, suggested (IV) as a more correct representation. This formula was accepted by Baeyer,¶ although he recognised that, in the absence of an asymmetric carbon atom, it did not permit of optical activity. He suggested, therefore, that possibly this might be due to the asymmetry of the whole molecule. Wallach, however, who had established the identity of *dl*-limonene and dipentene,** regarded this formula as incorrect, since he was unable to accept Baeyer's theory of an asymmetric molecule.



Baeyer and Wallach†† had based their formulae for limonene mainly on the fact that the hydrocarbon was formed by the dehydration of α -terpineol, which at the time was incorrectly represented by (V), although it was recognised that it was diffi-

* *Annalen*, 1886, 235, 67.

† *Ibid.* 1885, 18, 1733.

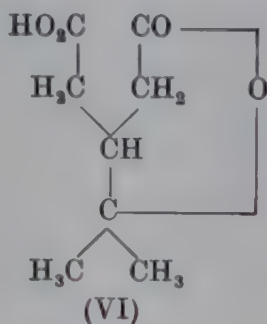
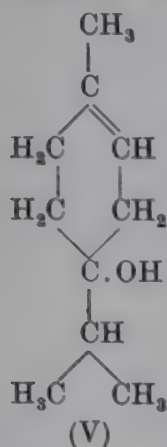
‡ *Ber.* 1894, 27, 1065.

§ *Annalen*, 1887, 239, 46.

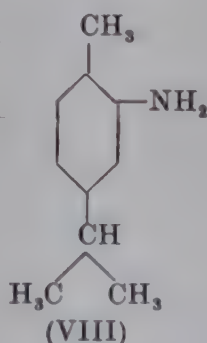
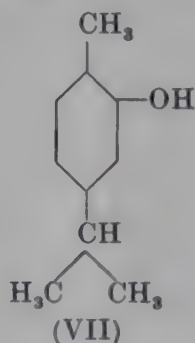
¶ *Ibid.* pp. 454, 3494.

†† Baeyer, *Ber.* 1894, 27, 440; Wallach, *Annalen*, 1893, 277, 144.

cult to reconcile this formula with the fact that on oxidation it gave the lactonic acid, *terpenylic acid* (VI).



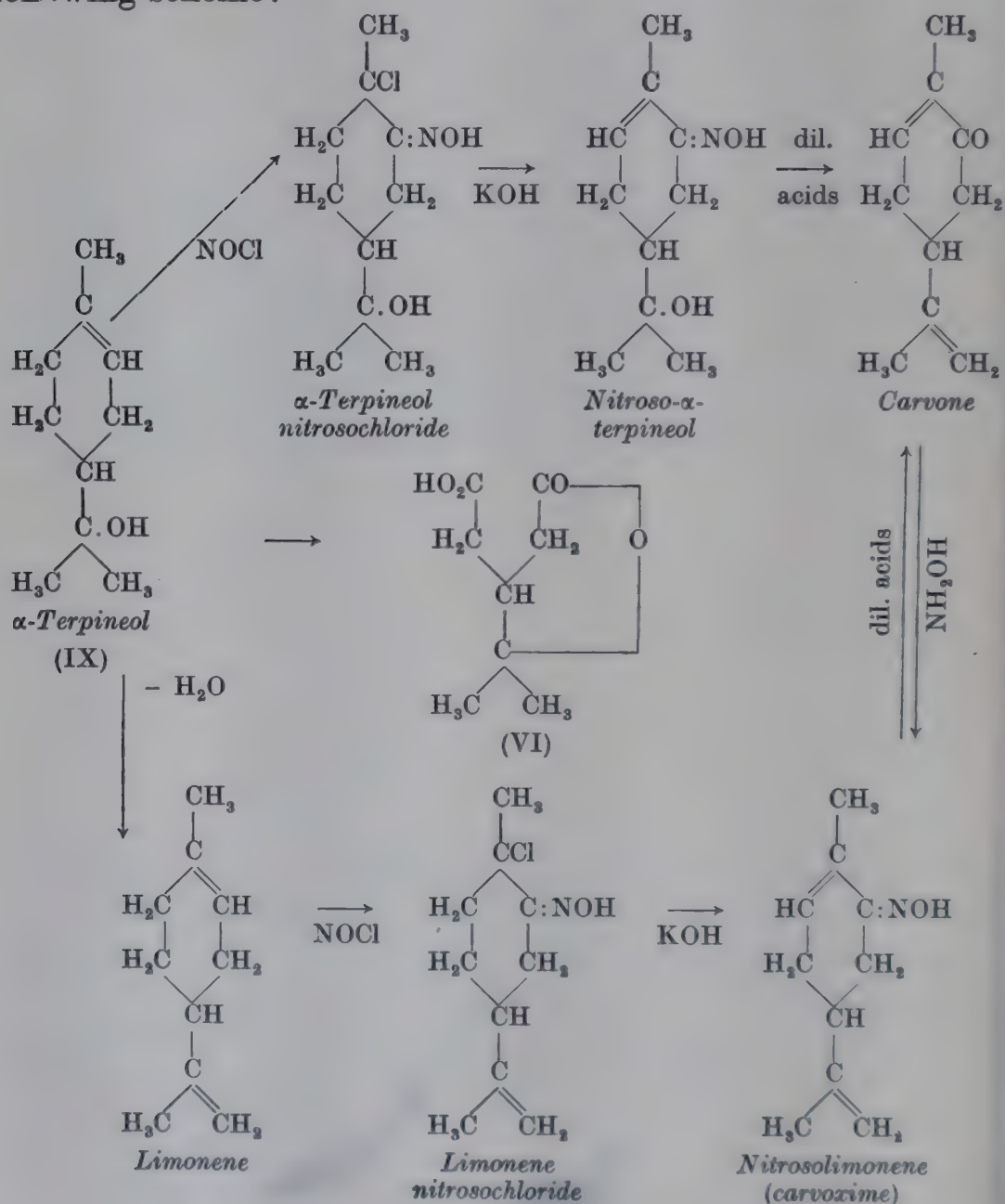
Goldschmidt had based his formulae for limonene on the relationship of the hydrocarbon to carvone, which was known to contain two ethylenic linkages, which were both assumed to be situated in the ring. This assumption seemed to be valid, since carvone could be converted readily into *carvacrol* (VII) and carvoxime into *carvacrylamine* (VIII), both derivatives of *p*-cymene, and the mobility of ethylenic linkages was not recognised at the time.



It was known also that α -terpineol and carvone were closely related. On oxidation carvone gives a hydroxy-lactonic acid which can be converted into terpenylic acid, and, further, the nitroso-derivative of α -terpineol, hydroxydihydrocarvoxime (formed by the action of alkali on α -terpineol nitrosochloride), gives with dilute acids carvone. It is obvious, therefore, that if α -terpineol be given the incorrect formula (V), the formation of limonene from this alcohol and the identity of carvoxime and nitrosolimonene are most simply explained by one of the formulae suggested by Goldschmidt, Wallach and Baeyer, the only im-

portant fact, difficult of explanation, being the formation of terpenylic acid.

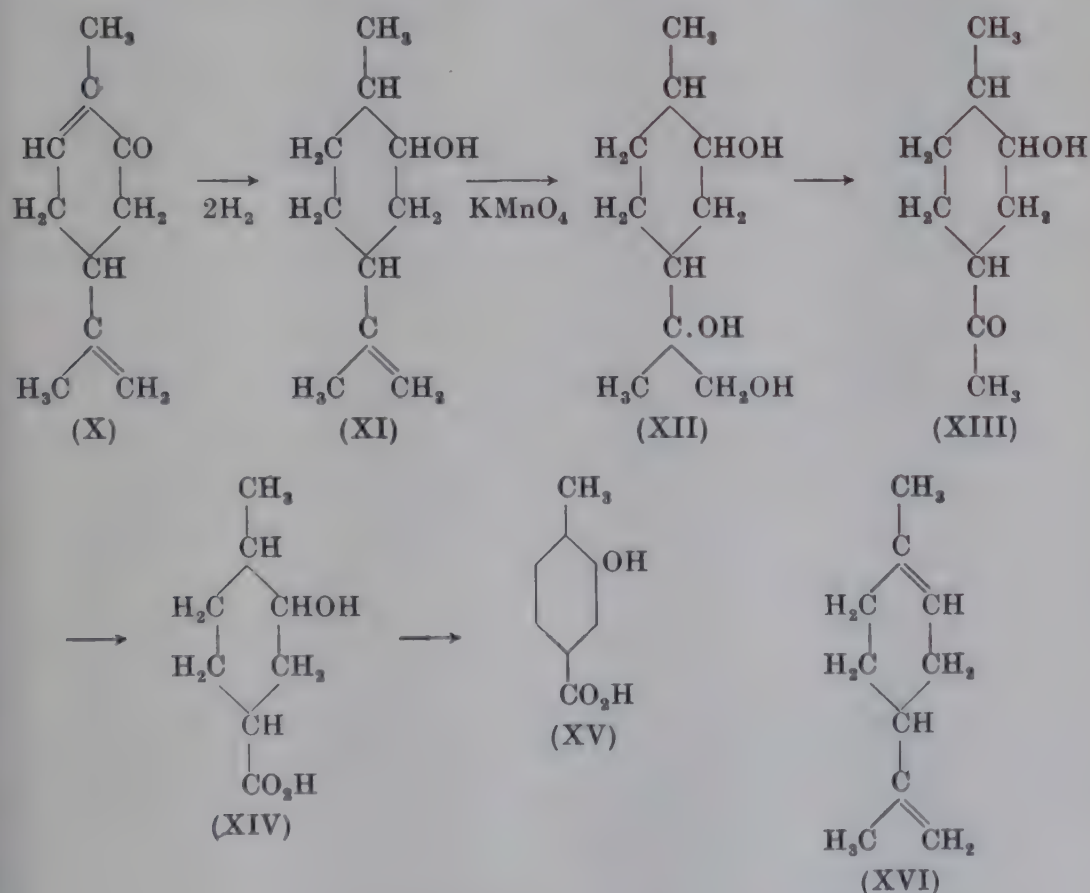
A correct explanation of the experimental results outlined above was due to Wagner.* He suggested that the correct formula for α -terpineol was (IX), which would account without any difficulty for the formation of terpenylic acid (VI) on oxidation. If this be accepted the various reactions to which reference has been made above proceed in accordance with the following scheme:



* Ber. 1894, 27, 1636, 2270.

Wagner did not offer any experimental proof of the formulae suggested, but this was provided very shortly afterwards by Tiemann and his collaborators.

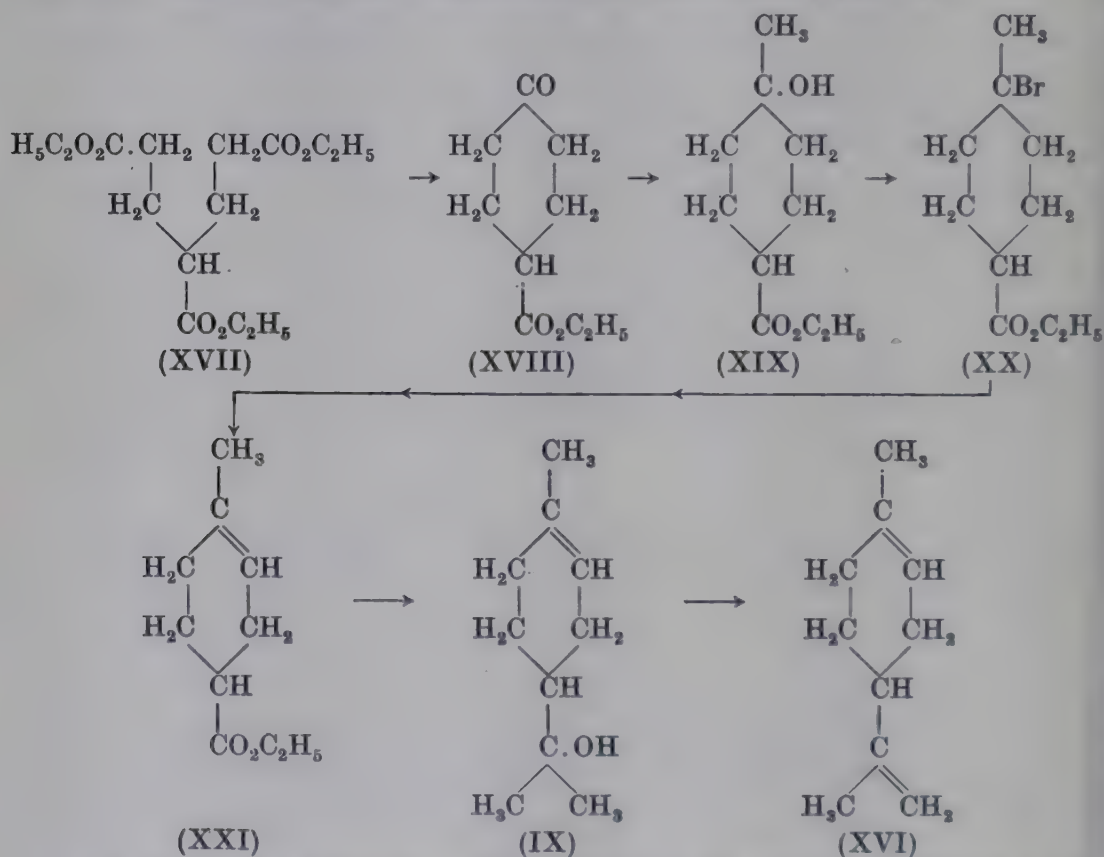
It had long been known (see p. 397) that carvone (X) gave on reduction an unsaturated secondary alcohol, *dihydrocarveol* (XI), containing one ethylenic linkage. By oxidation with potassium permanganate, Wallach* had converted this into a *trihydroxy-p-menthane* (XII) and, by methods to be described later, into the *ketone* (XIII). It was now shown that, when this ketone was oxidised with potassium hypobromite, a *hydroxy-acid* (XIV) was formed, which could be converted in its turn into 2-hydroxy-*p*-toluic acid (XV). These reactions, which can be formulated in accordance with the scheme set out below, leave no doubt of the presence of the *isopropenyl*-group in dihydrocarveol, which must therefore also be present in carvone and limonene. The position of the second ethylenic linkage in these substances is established by the formation of terpenylic acid from α -terpineol.



* *Annalen*, 1893, 275, 155; 277, 151.

The formulation of limonene as (XVI) is in complete agreement with all the properties of this important hydrocarbon, and it has been confirmed by the rational synthesis devised by W. H. Perkin, jun.* Perkin† prepared the cyclic ketonic acid, *cyclohexan-4-one-1-carboxylic acid* (XVIII), by treatment of the sodium salt of *pentane- $\alpha\gamma\epsilon$ -tricarboxylic acid* (XVII) with acetic anhydride.

The ester of this acid on treatment with methyl magnesium iodide gave the *hydroxy-ester* (XIX), from which the *bromo-ester* (XX) and the *unsaturated ester* (XXI) were prepared. When the latter was allowed to react with methyl magnesium iodide *dl- α -terpineol* (IX) was obtained. This was identical in all respects with the natural product and gave on dehydration with potassium hydrogen sulphate *dipentene* (*dl*-limonene) (XVI).



* In a long series of papers on "The Synthesis of the Terpenes", published in the *Journal of the Chemical Society*, Perkin and his collaborators described the synthesis of a number of derivatives of *o*-, *m*- and *p*-menthane. Much of the work lies outside the scope of this book, but an excellent summary has been provided by Perkin in a lecture given before the Pharmaceutical Society. This was published in *Perfumery and Essential Oil Record*, 1912, 3, 149.

† *J.C.S.* 1904, 85, 416. For a more convenient method see Kay and Perkin, *ibid.* 1906, 89, 1640.

In continuation of these experiments, Fisher and Perkin* attempted to prepare *d*- and *l*-limonene, starting from the *dextro*- and *laevo*-forms of the acid (XXI). They succeeded in synthesising the two active α -terpineols, but, on dehydrating these by any of the usual methods, almost complete racemisation was found to occur.

Although Perkin's is the only rational synthesis of dipentene, a number of indirect syntheses of the hydrocarbon have been carried out. The earliest was probably that due to Bouchardat† and Tilden,‡ who found that isoprene,§ prepared by the distillation of rubber,|| readily polymerised to dipentene. Dipentene is formed also, when a mixture of myrcene and isoprene or isoprene and the sesquiterpene, zingiberene,¶ are heated under pressure at 225°. Bertram and Walbaum** have shown that dipentene is obtained when linalool is treated with formic acid or dilute mineral acids.

Whilst limonene undoubtedly has the formula allotted to it, Escourrou†† claims to have proved, as the result of experiments on the oxidation of the hydrocarbon with ozone, that it always is a mixture of *limonene*, *terpinolene* and α -*terpinene*. The composition of the specimen examined by him was limonene 80 per cent., terpinolene 12 per cent. and α -terpinene 8 per cent. If future investigations should substantiate this, limonene would, like so many other members of the terpene group, be an inseparable mixture of isomeric hydrocarbons.

The physical constants, more especially the rotatory power, of limonene from natural sources, naturally show very considerable variations owing to a larger or smaller content of dipentene. The purest specimens of the active hydrocarbons, so far prepared, would appear to be those described by Braun and Lemke.** These were obtained from the pure tetrabromides by

* *J.C.S.* 1908, **93**, 1871.

† *Bull. Soc. chim.* 1875 [ii], **24**, 112.

‡ *J.C.S.* 1884, **45**, 410.

§ Isoprene was synthesised by Ipatiev, *J. pr. Chem.* 1897 [ii], **55**, 4, and by Euler, *ibid.* 1898 [ii], **57**, 132.

|| According to Staudinger and Fritsch, *Helv. Chim. Acta*, 1922, **5**, 797, dipentene is formed during the distillation of rubber in a yield of about 8 per cent.

¶ Semmler and Jonas, *Ber.* 1913, **46**, 1570, 1821.

** *J. pr. Chem.* 1892 [ii], **45**, 590.

†† *Bull. Soc. chim.* 1928 [iv], **43**, 1204.

** *Ber.* 1923, **56**, 1652; compare Godlewski and Roshanowitsch, *J. Russ. Phys. Chem. Soc.* 1899, **31**, 209.

treatment with magnesium in ethereal solution and they quote the following constants:

d-limonene, b.p. 176–176.4°, $d_4^{20^\circ}$ 0.8411, $[\alpha]_D^{20^\circ} + 126.84^\circ$;
l-limonene, b.p. 176–176.4°, $d_4^{20^\circ}$ 0.8422, $[\alpha]_D^{20^\circ} - 122.6^\circ$.

A very carefully purified specimen of *d*-limonene from cummin oil was found by Brühl* to have b.p. 175.5–176°/763 mm., $d_4^{21^\circ}$ 0.8402, $n_D^{21^\circ}$ 1.4743, $[\alpha]_D^{19.5^\circ} + 123.8^\circ$, whilst for *l*-limonene from the oil of the cones of the silver fir (*Abies pectinata*) he found b.p. 175.5–176.5°/763 mm., $d_4^{20.5^\circ}$ 0.8407, $n_D^{21^\circ}$ 1.474, $[\alpha]_D^{19.5^\circ} - 101.3^\circ$. More recently, Richter and Wolff† have shown that dipentene boils at 178.0°/760 mm., whilst for the limonenes they found the values: *d*-limonene, b.p. 177.6–177.8°/755 mm., $n_D^{17^\circ}$ 1.473, $[\alpha]_D + 124^\circ$; *l*-limonene, b.p. 177.6–177.8°/755 mm., $d_4^{20.6^\circ}$ 0.8417, $n_D^{17.2^\circ}$ 1.4727, $[\alpha]_D - 121^\circ$.

When prepared by the dehydration of α -terpineol, dipentene, owing to the presence of impurities, is usually found to have a somewhat higher boiling-point, 180–181°, than *d*- (and *l*-) limonene. Brühl found, however, that when prepared by the admixture of the active hydrocarbons, the boiling-point and other constants, apart from the rotatory power, were unchanged: b.p. 175.5–176.5°/763 mm., $d_4^{20.85^\circ}$ 0.8402, n_D 1.4744, $[\alpha]_D \pm 0^\circ$.

Whilst Brühl's results show a slight exaltation for the molecular refraction (obs. 45.53, calc. 45.24), the value (45.23) obtained by Perkin and Wallach‡ is normal. It is possible that this slight difference may be due to the difficulty of preparing limonene absolutely free from isomerides.

Rule and Chambers§ have determined the rotatory power of *d*-limonene in a number of different solvents.

The Raman spectrum of limonene has been investigated by Jatkar and Padmanabhan|| and by Marot,¶ and the absorption spectrum has been studied by Crymble, Stewart, Wright and Rea.** The X-ray haloes of *d*-limonene and dipentene, using Cu K_α radiation, have been described by Vaidyanathan.††

* *J.C.S.* 1907, **91**, 121.

† *Ber.* 1930, **63**, 1724.

‡ *J.C.S.* 1910, **97**, 1437.

§ *Ibid.* 1937, p. 152.

|| *Indian J. Physics*, 1936, **10**, 55.

¶ *Bull. Inst. Pin*, 1933 (2), **38**, 61.

** *J.C.S.* 1911, **99**, 1267; compare Hantzsch, *Ber.* 1912, **45**, 553, 1743, and Auwers, *ibid.* p. 963.

†† *Indian J. Physics*, 1929, **3**, 387.

Limonene is a comparatively stable hydrocarbon. It can be distilled at the ordinary pressure without decomposition, but, like all terpenes, it is somewhat readily oxidised on exposure to the air (see below). When heated with sulphur* it yields *p*-cymene, and a sulphide, $C_{10}H_{16}S$, whilst it is decomposed by hot metal filaments, giving a good yield of isoprene.† On warming with mineral acids conversion into terpinene has repeatedly been observed, accompanied, as a rule, by some conversion into *p*-cymene.‡ This isomerisation into terpinene probably occurs when limonene is heated with maleic acid, since Hultzsche§ has shown that the product formed is the maleic anhydride adduct of α -terpinene. With maleic anhydride itself, limonene would not be expected to react readily, since it contains no conjugated system of ethylenic linkages, but according to Hultzsche it gives, in poor yield, an acid $C_{14}H_{20}O_4$, m.p. 147° , of unknown structure, which forms an anhydride, m.p. 42° .

Although, according to Semmler,|| limonene cannot be reduced by sodium and alcohol, addition of hydrogen readily takes place in the presence of catalysts. Using a nickel catalyst at 180° , Sabatier and Senderens¶ obtained *p*-menthane, whilst with copper** at the same temperature Δ^1 -*p*-menthene was formed; at a higher temperature (350 – 360°), however, dehydrogenation with formation of *p*-cymene was observed.†† Hydrogenation with a platinum black catalyst has been carefully studied by Vavon,** who, by following the reaction either polarimetrically or by the rate of hydrogen absorption, was able to prepare either Δ^1 -*p*-menthene or *p*-menthane. The former was prepared in a high state of purity, b.p. 175 – 177° , $d_4^{18} 0.8246$, $n_D 1.4563$, $[\alpha]_{4360} + 234^\circ$. Hydrogenation under pressure has been shown by Ipatiev§§ to lead to a mixture of the two hydrocarbons mentioned above. By passing limonene in a current of carbon dioxide over palladinised asbestos at 180 – 185° , Zelinski||| observed that hydrogenation

* Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 346; Nakatsuchi, *J. Soc. Chem. Ind. Japan*, 1930, 33, 408 B; 1932, 35, 376 B.

† Staudinger and Klever, *Ber.* 1911, 44, 2213.

‡ Compare Wallach, *Annalen*, 1887, 239, 15.

§ *Ber.* 1939, 72, 1173.

|| *Ibid.* 1901, 34, 3125.

¶ *Compt. rend.* 1901, 132, 1256.

** *Ibid.* 1902, 134, 1130.

†† Sabatier and Gaudion, *ibid.* 1919, 168, 671.

‡‡ *Bull. Soc. chim.* 1914 [iv], 15, 282; compare Willstätter and Waldschmidt-Leitz, *Ber.* 1921, 54, 125.

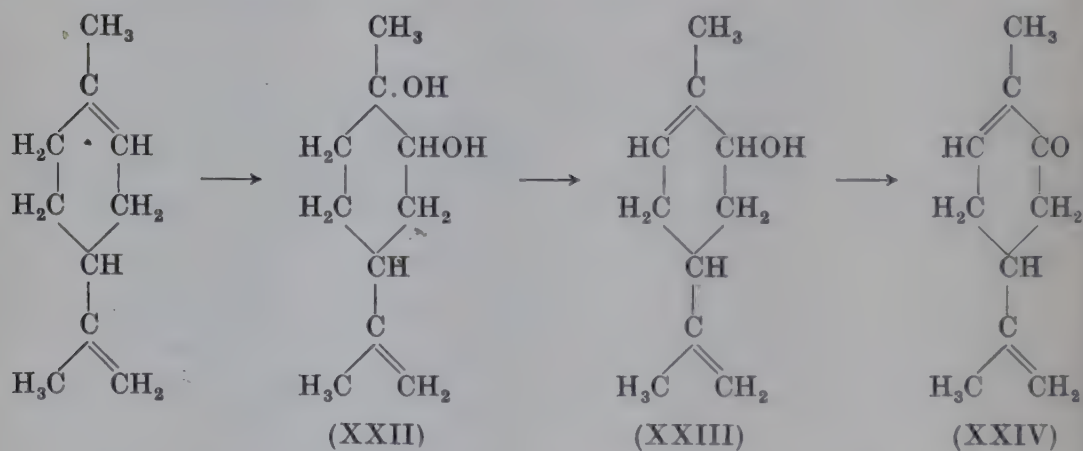
§§ *Ber.* 1910, 43, 3547.

||| *Ibid.* 1924, 57, 2058.

and dehydrogenation took place simultaneously, *p*-menthane and *p*-cymene being formed. A similar result is obtained when limonene is boiled over platinised charcoal.*

The oxidation of limonene under varying conditions has been studied very thoroughly. Blumann and Zeitschel[†] have shown the oxidation of the terpene in moist air to proceed in a somewhat unexpected manner, the products being *dl*-carveol (XXIII) and *dl*-carvone (XXIV). It must be presumed that the primary product of the reaction is the glycol (XXII), from which the alcohol is formed by loss of water.

In this connection it is interesting to note that, according to Sword,[‡] the glycol, $\Delta^{8(10)}$ -*p*-menthene-1:2-diol (XXII), forms the main product of the reaction when *d*-limonene is oxidised with hydrogen peroxide in acetic acid solution.



As was to be anticipated, oxidation with ozone, which has been studied by Harries and Adam,[§] leads to the *diketonic acid* (XXV), an acid previously obtained by Tiemann and Semmler (see below). This acid is unstable, and on esterification or treatment with alkali undergoes cyclisation with formation of an unsaturated *ketonic acid*, which must be represented by either (XXVI) or (XXVI a).

Limonene may also be ozonised in the vapour phase.^{||}

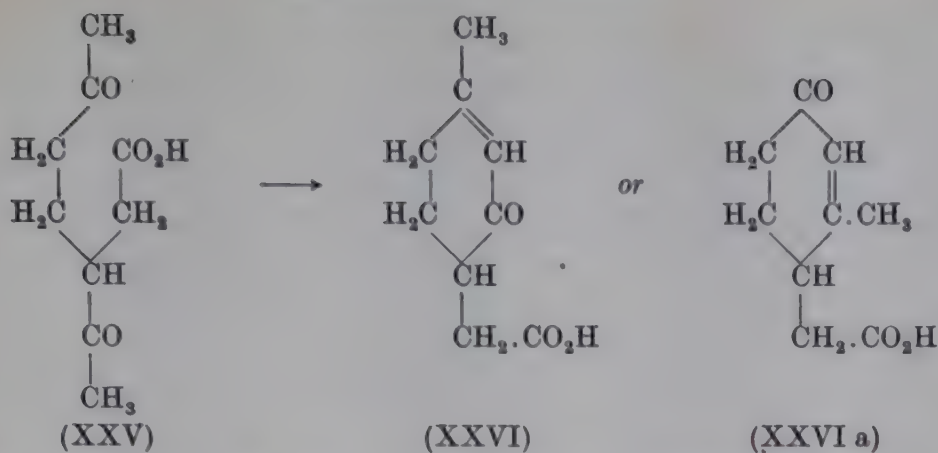
* Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

† *Ber.* 1914, 47, 2623; compare Dupont, *Ind. chim. belge*, 1940, 11, 3.

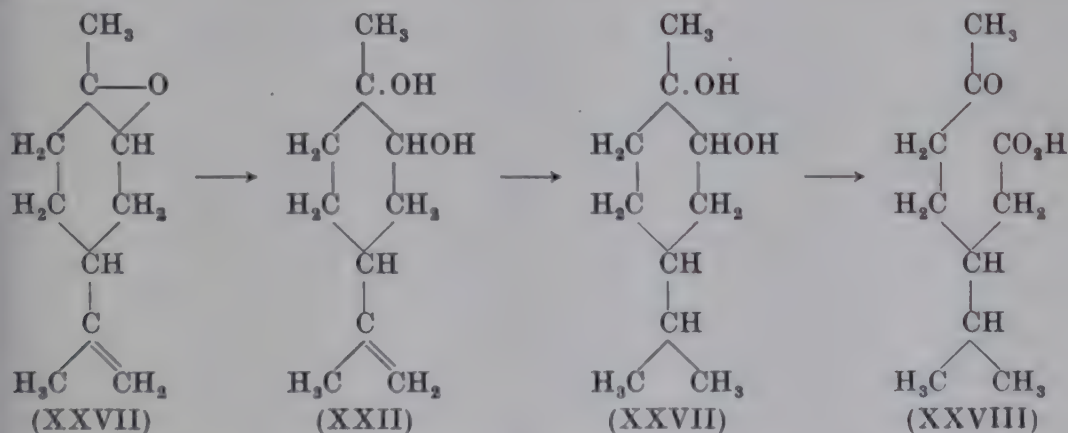
‡ *J.C.S.* 1925, 127, 1632.

§ *Ber.* 1916, 49, 1034.

|| Spencer, Weaver, Oerriecht, Sykes, Barney and Elder, *J. Org. Chem.* 1940, 5, 610.



The oxidation of the terpene with perbenzoic acid was first studied by Prileschaev,* who described the preparation of a *monoxide* and *dioxide*. More recently the reaction has been investigated by Meerwein,† who has shown the first product of the reaction to be *limonene monoxide* (XXVII), b.p. 82–84°/14–15 mm., d_4^{20} 0.929, n_D^{20} 1.4697, $[\alpha]_D^{20} + 67.37^\circ$, which on hydration with sulphuric acid (1 per cent.) gives the *glycol* (XXII), which can be catalytically hydrogenated to the saturated *glycol* (XXVIII). The position of the hydroxyl groups was established by oxidation of the latter to β -isopropyl- δ -acetyl-n-valeric acid (XXIX).



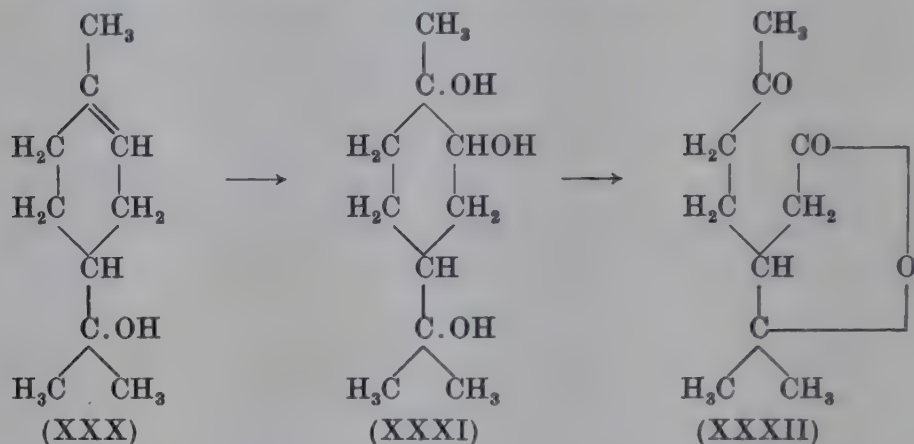
Henderson‡ has described an additive compound, $\text{C}_{10}\text{H}_{16}$, $2\text{CrO}_2\text{Cl}_2$, which is formed when chromyl chloride is added to limonene in carbon disulphide solution. On decomposition with water, this yields a mixture of α -*p*-tolyl propaldehyde and *p*-tolyl methyl ketone, so that dehydrogenation to *p*-cymene takes place prior to oxidation.

* Ber. 1909, 42, 4814.

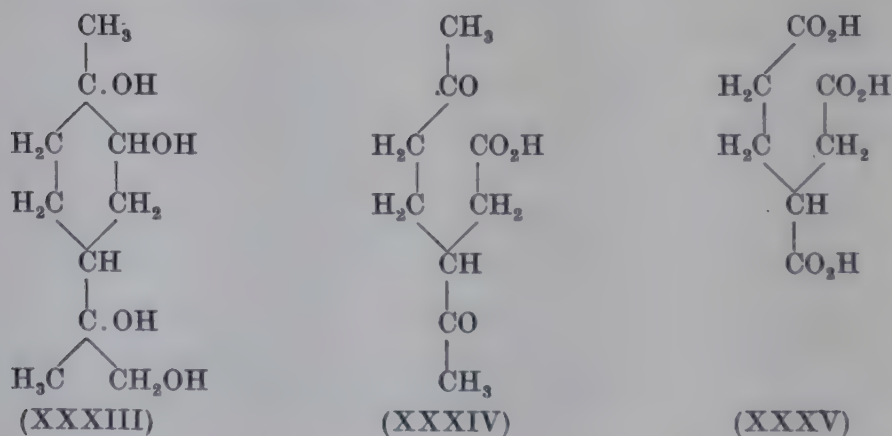
† J. pr. Chem. 1926 [ii], 113, 19.

‡ J.C.S. 1907, 91, 1871; compare Henderson and Cameron, *ibid.* 1909, 95, 971.

Oxidation of the terpene with Beckmann's chromic acid mixture has been investigated by Henry and Paget.* They consider it probable that the first product of the reaction is α -terpineol (XXX), which is then oxidised to the *glycerol* (XXXI), m.p. 122°, and finally to the *ketolactone* (XXXII).



The oxidation of limonene with potassium permanganate was first carefully investigated by Wagner,[†] who, working in very dilute solution, succeeded in preparing the alcohol *p*-menthane-1:2:8:9-tetrol (XXXIII) (limonetrile), m.p. 191.5–192°. The further degradation of this substance was studied by Tiemann and Semmler,[‡] who obtained from it the *diketonic acid* (XXXIV) from which, by the action of sodium hypobromite, they prepared the *tricarboxylic acid* (XXXV).



The products formed by the oxidation of limonene with potassium permanganate were also examined by Godlewski,[§]

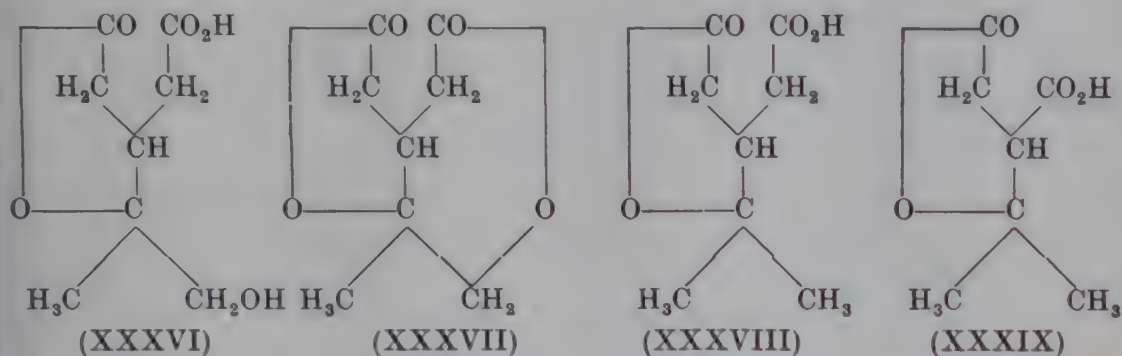
* J.C.S. 1928, p. 71.

† Ibid. 1895, 28, 2150.

‡ Ber. 1890, 23, 2315.

§ J. Russ. Phys. Chem. Soc. 1899, 31, 211.

who succeeded in separating in an excellent yield the *dilactone* (XXXVII), m.p. 129–130°, which is formed from the *hydroxy-terpenylic acid* (XXXVI) by loss of water. The latter acid can readily be converted into *terpenylic acid* (XXXVIII), whilst it may be mentioned that Archanguelski* has also separated the lower homologue, *terebic acid* (XXXIX), from amongst the products of the oxidation of limonene. The bearing of the formation of terpenylic and terebic acids on the determination of the constitution of limonene has already been referred to.



The oxidation of dipentene with lead tetra-acetate gives a mixture of products, of unknown structures.†

Whilst the action of chlorine on limonene does not lead to very well-defined products and need not be discussed,* as has been mentioned already the bromides are of great importance. Since *d*-limonene tetrabromide was first prepared by Wallach,§ its preparation has been frequently described by other investigators. In order to obtain a crystalline product, it is essential that the reagents used should not be completely anhydrous, otherwise only oily products are obtained. The tetrabromide is probably prepared most conveniently by the method suggested by Baeyer and Villiger,|| who brominated the terpene in amyl alcohol-ether solution. On slow evaporation of the ether well-formed crystals are obtained. It is possible that the tendency for the formation of liquid bromides is due to the occurrence of *cis-trans*-isomerism, but no direct proof of this has been furnished. The optically active *tetrabromides*, m.p. 104–105°, crystallise best from ethyl acetate; in chloroform solution, they have a rotation of $[\alpha]_D \pm 73$

* *Bull. Soc. chim.* 1895 [iii], 14, 1387.

† Ward, *J. Amer. C.S.* 1938, 60, 325.

‡ Compare Wallach and Hesse, *Annalen*, 1891, 264, 32; 1892, 270, 196.

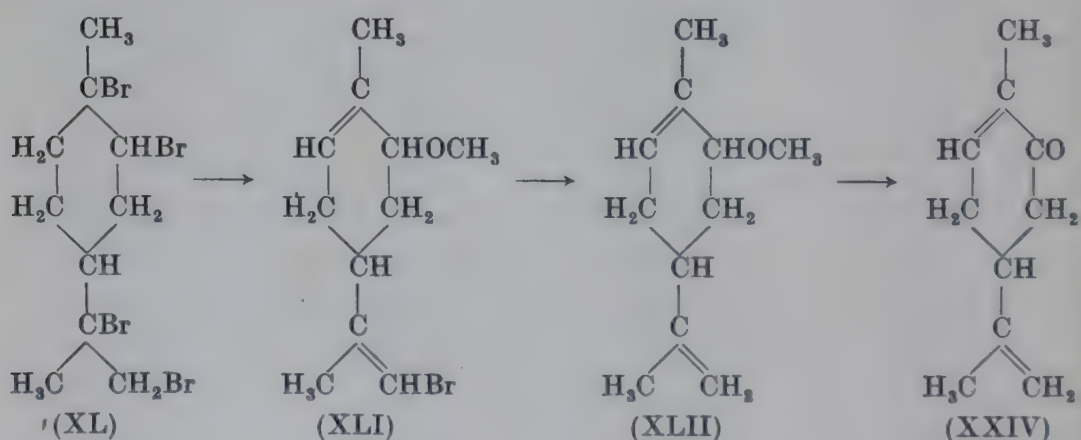
§ *Ibid.* 1884, 225, 318.

|| *Ber.* 1894, 27, 448.

to 74° , the rotatory power being of the same sign as that of the hydrocarbon from which they are respectively prepared.

By the bromination of dipentene, or by mixing equal quantities of *d*- and *l*-limonene tetrabromides, *dipentene tetrabromide* is obtained. This substance was probably first prepared in an impure state by Schmidl* and fairly pure by Renard† who gives the melting-point as 120° . It was first obtained pure by Wallach‡ by the bromination of cineole and later by the bromination of "cinene" (dipentene). The tetrabromide crystallises in rhombic prisms, m.p. $125\text{--}126^\circ$.

The reactions of the optically active and externally compensated tetrabromides, which are identical, have been studied in some detail. Reference has already been made (p. 152) to its reconversion into the hydrocarbon by reduction with magnesium in ethereal solution or by zinc in alcoholic solution. With sodium methoxide, Wallach§ found that a *monobromide* (XLI) was formed, which, on reduction with sodium and alcohol, gave the *methyl ether* (XLII) from which, on oxidation with chromic acid, carvone (XXIV) was obtained. The monobromide is optically inactive whether prepared from limonene or dipentene tetrabromides (XL).



If limonene is treated with hydrogen chloride, under conditions which exclude all traces of moisture, a *monohydrochloride* is obtained, which is optically active in the same direction as the

* *Jahresbericht*, 1860, p. 480.

† *Ann. chim.* 1884 [vi], 1, 245.

‡ *Annalen*, 1887, 239, 11; 1891, 264, 16; 1893, 275, 109; 1894, 281, 127; 1902, 324, 86.

§ *Ibid.* 1884, 225, 304.

terpene from which it is prepared. Riban* originally prepared this substance and it was more thoroughly investigated by Wallach and Kremers,† who were the first to observe the necessity for eliminating all traces of moisture. The hydrochloride has b.p. 97–98°/11–12 mm., $d_{17.8}^{17.8}$ 0.973, $[\alpha]_D + 39.5^\circ$ and -40.0° . According to v. Braun and Werner,‡ the monohydrochloride is rapidly isomerised by hydrogen chloride in carbon disulphide solution, the rotatory power falling from $[\alpha]_D + 75$ to -33° in 13 hours.

Semmler§ showed that the hydrochloride must be represented by formula (XLIII), since it could be converted into α -terpineol. The same author observed also that on reduction with sodium and alcohol at 10°, Δ^1 -*p*-menthene was formed, whilst with the same reagents in boiling solution, limonene resulted.||

The corresponding *monohydrobromide* has been prepared by Bacon,¶ b.p. 106–109°/10 mm., d_4^{30} 1.1211, n_D^{30} 1.5012, by the action of hydrogen bromide on limonene in light petroleum solution.

If hydrogen chloride is allowed to react with either *d*- or *l*-limonene or dipentene, under conditions which allow access of moisture, *dipentene dihydrochloride* is obtained. This dihydrochloride was first prepared by Thenard** and has since been described by numerous investigators. It is most conveniently prepared by the saturation of a well-cooled solution of the terpene in acetic acid with hydrogen chloride. When prepared in the usual manner and recrystallised from methyl alcohol, it has m.p. 49–50°. As was first pointed out by Baeyer,†† this is probably the *trans*-form, since, if the dihydrochloride is prepared from cineole at a low temperature, a second modification can be obtained, which melts at 25°. The two forms may be represented by (XLV) and (XLVI).

When the dihydrochloride is shaken with dilute alkali, it yields a mixture of dipentene, α -terpineol, *cis*- and *trans*-terpin (see p. 302),‡‡ whilst, when digested with aniline§§ or with sodium

* *Compt. rend.* 1874, **79**, 223; *Bull. Soc. chim.* 1874 [ii], **22**, 245; *Ann. chim.* 1875 [v], **6**, 216.

† *Annalen*, 1892, **270**, 188.

‡ *Ibid.* 1895, **28**, 2189.

¶ *Philippine J. Sci.* 1909, **4**, 105.

†† *Ber.* 1893, **26**, 2861.

** Wallach, *Annalen*, 1906, **350**, 154.

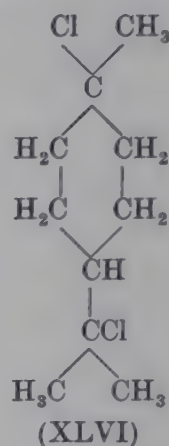
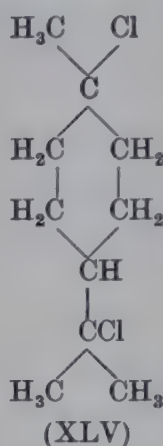
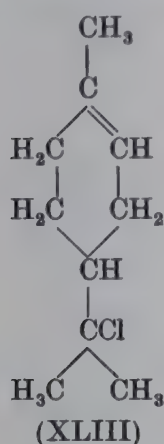
* *Ber.* 1929, **62**, 1056.

|| *Ibid.* 1903, **36**, 1036.

‡‡ *Mémoires d'Arcueil*, **2**, 32.

§§ Wallach, *ibid.* 1885, **227**, 286.

acetate in acetic acid solution, dipentene is obtained. On prolonged boiling with alcohol, it is decomposed with formation of α -terpinene. By treatment with chlorine a *trichloride*, m.p. 87° , is obtained.* Roberts† has shown more recently that, by the action of "molecular" silver, the dihydrochloride is converted into a *diterpene*, b.p. $173\text{--}183^\circ/10\text{ mm.}$, d^{20}_D 0.9361, n^{20}_D 1.5170.



Dipentene dihydrobromide has been prepared in a similar manner to the dihydrochloride and like this exists in both *cis*- and *trans*-modifications. The *cis*-form was first prepared in a pure state by Baeyer by the action of hydrogen bromide on cineole and was shown by him to crystallise in leaflets, m.p. $38\text{--}40^\circ$. The *trans*-form, which is that usually obtained, crystallises in rhombic plates, m.p. 64° . On treatment with bromine a *tribromide*, m.p. 110° , is formed;‡ some of the reactions of this substance are referred to on p. 167 in discussing the chemistry of terpinolene.

The *cis*- and *trans*-forms of the *dihydroiodide* have also been prepared, the former melting at 50° and the latter at $78\text{--}79^\circ$.

Limonene can be hydrated readily to α -terpineol (XLIV), the acetate of the alcohol being obtained when the hydrocarbon is shaken with a dilute solution of sulphuric acid in acetic acid. At the same time some terpin hydrate (XLVII) is also formed. According to Aschan§ the latter is obtained in excellent yield by treatment of the terpene with sulphuric acid (50 per cent.) at -6° , although, as Brooks and Humphrey|| have found, concen-

* Wallach, *Annalen*, 1892, **270**, 196.

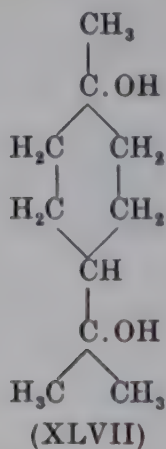
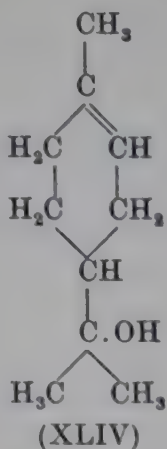
† Wallach, *Annalen*, 1891, **264**, 25.

|| *J. Amer. C.S.* 1918, **40**, 844.

‡ *J.C.S.* 1925, **127**, 2451.

§ *Chem. Zentr.* 1919, **1**, 284.

trated sulphuric acid causes polymerisation to high-boiling products.



Attention has already been directed to the great importance in terpene chemistry of limonene nitrosochloride, first prepared by Tilden by the action of gaseous nitrosyl chloride on limonene. The preparation and properties of *limonene nitrosochloride* were subsequently investigated by Wallach,* who very much improved the method of preparation by using, in place of gaseous nitrosyl chloride, amyl or ethyl nitrite in the presence of hydrochloric acid. It was soon discovered that the nitrosochloride was a mixture of the two forms, α -limonene nitrosochloride and β -limonene nitrosochloride, which could be separated by fractional crystallisation from either ether or acetone.† The corresponding racemic forms have also been prepared, but show much less tendency to crystallise.

Wallach and Conrad† gave the following constants for the active forms, the rotatory powers being observed in chloroform solution.

	d- (or l-) <i>Limonene</i>	<i>dl-</i>	<i>d-</i>	<i>l-</i>
	m.p.	m.p.	$[\alpha]_D$	$[\alpha]_D$
α -Nitrosochloride	103–104°	78°	+ 313.4°	– 314.8°
β -Nitrosochloride	105–106°	—	+ 240.3°	– 242.2°

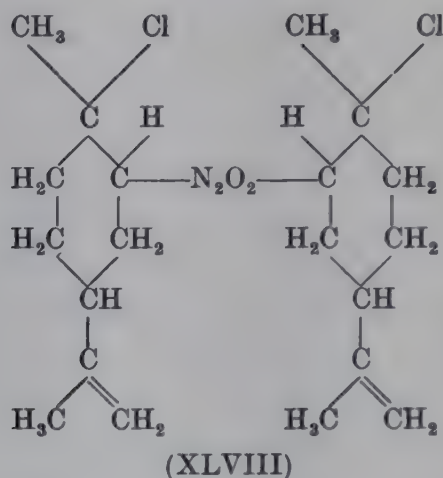
The constitution of the nitrosochlorides and the relationship of α - and β -forms to one another were not determined by either Tilden or Wallach, although Tilden expressed the opinion that

* *Annalen*, 1888, 245, 255 and subsequent papers.

† *Ibid.* 1889, 252, 110; 1904, 336, 43; compare Leach, *J.C.S.* 1905, 87, 417.

* *Annalen*, 1889, 252, 145.

they contained a true *nitroso*-group. This view was difficult however to accept since the nitrosochlorides were insoluble in alkali. Baeyer* showed later that both nitrosochlorides were bimolecular, although they tended to dissociate in dilute solution. He represented them therefore by formula (XLVIII). Whilst this formula explained satisfactorily the reactions of the nitrosochlorides, it left undecided their relationship to one another.†



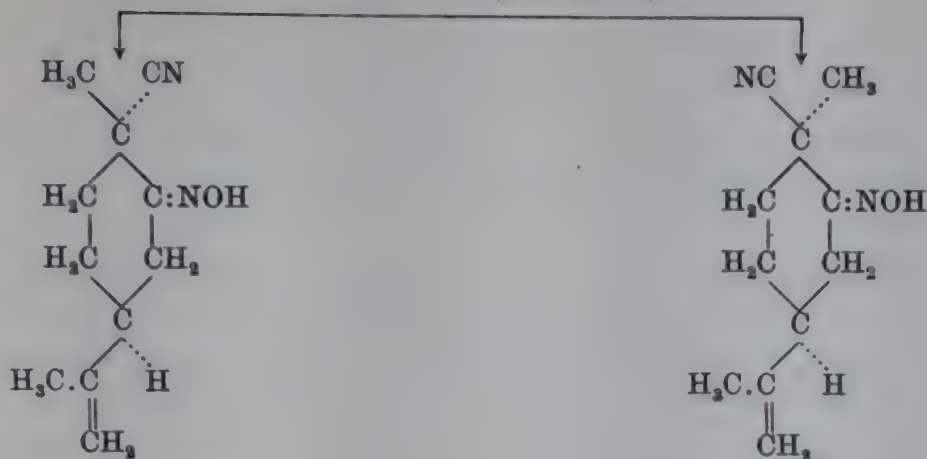
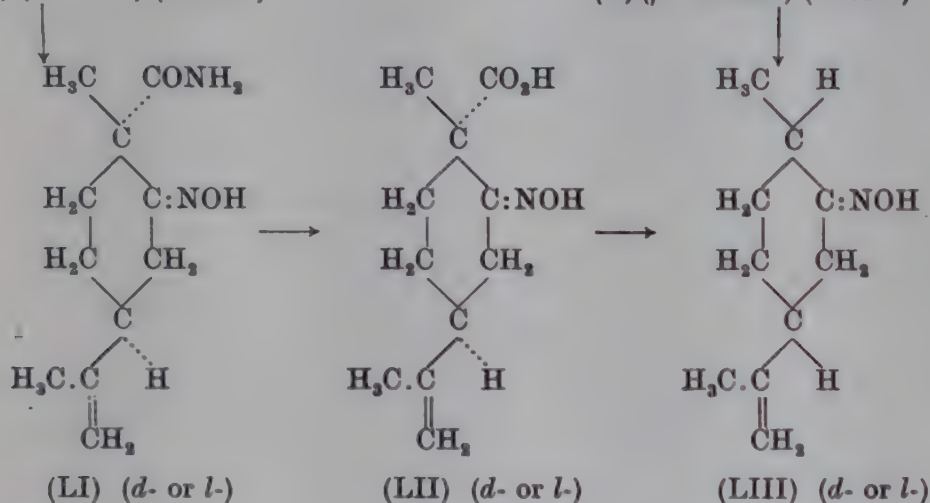
This has been determined by the investigations of Leach,‡ working in Tilden's laboratory. He showed that when either the α - or β -nitrosochloride is treated with potassium cyanide, they *both* yield the same two isomeric *nitrosocyanides*, designated α - and β -modifications, (XLIX) and (L). The α -cyanide behaves normally, yielding on hydrolysis the corresponding *amide* (LI) and *acid* (LII) which, by loss of carbon dioxide, yields *dihydrocarvoxime* (LIII). The β -nitrosocyanide could not be examined in detail, but it was shown to yield the same *oxime* (LIII). The exact mechanism of the conversion of the nitrosochlorides into the nitrosocyanides was not determined, but the changes involved can be represented best as shown below, the nitrosochlorides being *cis-trans*-isomerides.

The recognition of the α - and β -nitrosochlorides as bimolecular *cis-trans*-isomerides accounts readily for the properties of these

* *Ber.* 1895, **28**, 652.

† The actual nature of the linking between the two molecules has not been determined; that shown above is regarded as probable by Tilden and Shephard, *J.C.S.* 1906, **89**, 923.

‡ *Ibid.* 1905, **87**, 413.

(XLVIII) α and β (*d*- and *l*-)(XLIX) ($\alpha = \text{cis-}$) (*d*- or *l*-)(L) ($\beta = \text{trans-}$) (*d*- or *l*-)

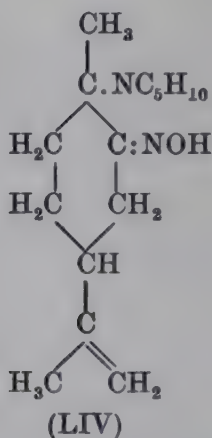
substances. By the action of alkali on the nitrosochloride, carboxime results and this reaction probably takes place in two stages, the bimolecular nitrosochloride passing first into the monomolecular form (*carboxime hydrochloride*), which then loses hydrogen chloride with the formation of carboxime.* The oximes prepared from the optically active nitrosochlorides are active, but optically opposite in sign to the nitrosochloride from which they are prepared. According to Deussen and Hahn,[†] in addition to the ordinary carboxime, a second carboxime is formed in this reaction. The nature of the relationship between these two oximes does not appear to have been determined, but they are presumably the *syn*- and *anti*-forms. By the action of the Grignard reagent on the nitrosochlorides, Tilden and

* Baeyer, *Ber.* 1896, 29, 8.† *Ibid.* 1910, 43, 519.

Shepherd* obtained two isomeric substances of the formula $C_{20}H_{32}ON_2Cl_2$; they were unable to determine the constitution of these substances, which showed remarkable stability.

Limonene nitrosate, which is also bimolecular, was prepared by Wallach† and is very low melting; *dipentene nitrosate* has m.p. 84° .

With organic primary or secondary bases the nitrosochlorides and the nitrosate react to give well-defined crystalline nitrolamines, which are monomolecular, and are very suitable for the characterisation of the parent hydrocarbon. Since there are six nitrosochlorides, namely the *d*- and *l*- and *dl*- α -nitrosochlorides and the *d*- and *l*- and *dl*- β -nitrosochlorides, six corresponding nitrolamines can be prepared. As typical of these, the constants of the *limonene nitrolpiperidides* represented by (LIV) are given in the appended table.



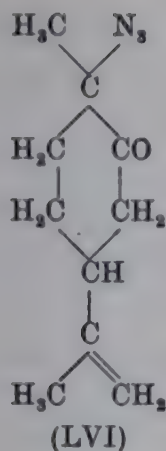
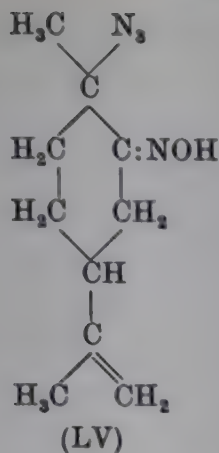
<i>d</i> -Limonene		<i>l</i> -Limonene		<i>Dipentene</i>
$[\alpha]_D$	m.p.	$[\alpha]_D$	m.p.	m.p.
+ 67.5°	93–94°	– 67.6°	93–94°	154°
+ 60.48°	110–111°	– 60.18°	110–111°	152°

Forster and van Gelderen‡ have described an interesting substance, a *nitrosoazide* (LV), which is formed when either dipentene nitrosochloride or nitrosate is treated with sodium azide. On treatment with an alcoholic solution of sodium hydroxide it is converted into carboxime, whilst with mineral acids the *triazoketone* (LVI) is formed. This latter yields with hydroxylamine the original nitrosoazide. Analogous substances were prepared from *d*- and *l*-limonene.

* *J.C.S.* 1906, **89**, 921.

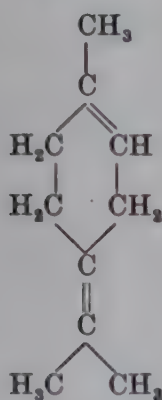
† *J.C.S.* 1911, **99**, 2059.

‡ *Annalen*, 1888, **245**, 258, 270.



TERPINOLENE

($\Delta^{1:4(8)}$ -*p*-Menthadiene or
1-Methyl-4-isopropylidene- Δ^1 -cyclohexene)



Although terpinolene has long been known, its presence in essential oils has only been established comparatively recently. According to Clover* it occurs in Manila elemi, whilst Schimmel and Co.† state that it is probably present in coriander oil. Escourrou‡ has suggested that *d*-limonene obtained from oil of sweet oranges contains about 12 per cent. of terpinolene, and it has recently been shown to occur in the essential oil of *Cupressus macrocarpa*.§

A mixture of hydrocarbons containing terpinolene was probably first prepared by Deville|| by the action of various acids on

* *Philippine J. Sci.* 1907, **2**, 17; compare Bacon, *ibid.* 1909, **4**, 93.

† *Schimmel's Report*, 1909, Oct. p. 33.

‡ *Chim. et Ind.* 1925, **14**, 519; *Bull. Soc. chim.* 1928 [iv], **43**, 1204.

|| Briggs and Sutherland, *J. Org. Chem.* 1942, **7**, 397.

§ *Ann. chim.* 1840 [ii], **75**, 37, 79; *Annalen*, 1841, **37**, 178; 1849, **71**, 351.

pinene. This mixture, terebene, was recognised by its discoverer, and later by Berthelot and Riban,* as different from pinene and limonene, whilst Riban showed that it contained *p*-cymene. Subsequently Armstrong and Tilden† found that terebene contained camphene and, in addition, a hydrocarbon, which they regarded as homogeneous and called *terpinylene* or *terpilene*. This terpene they prepared also by the action of heat or aniline on limonene dihydrochloride, by treatment of terpin with dilute sulphuric acid, and by the action of concentrated sulphuric acid on camphene. Terpinylene, b.p. 175–178°, d^{15}_4 0.8526, was also studied by Lauth and Oppenheim‡ and Walitzki.§

The early attempts of Tilden to prepare crystalline derivatives from terpinylene were not successful. The nitrosochloride was an oil, whilst bromine in chloroform solution gave a liquid dibromide, which, on warming, lost hydrogen bromide with the formation of *p*-cymene.

In 1884 Wallach|| began his classical investigations in terpene chemistry by a study of the mixture of hydrocarbons resulting from the action of acids on pinene (oil of turpentine). He found that when pinene was treated with an alcoholic solution of sulphuric acid, in addition to limonene or dipentene another hydrocarbon, b.p. 179–190°, was formed. To this hydrocarbon he gave the name *terpinolene*, and he characterised it by the preparation of a crystalline *tetrabromide*, m.p. 116°, isomeric with, but entirely different from, limonene or dipentene tetrabromides.¶ With the discovery of this new derivative, it was shown that terpinolene was formed when terpin, α -terpineol, cineole, etc., were treated with dilute acids.** Wallach further made the important observation that terpinolene, which he regarded as homogeneous, gave, on treatment with hydrogen chloride in acetic acid solution, dipentene dihydrochloride.

Later investigations led Wallach to doubt the homogeneity of the hydrocarbon, since he found that when terpinolene was prepared by the action of sulphuric acid on terpin hydrate, terpinene was always present. He observed also that it was

* *Ann. chim.* 1875 [v], 6, 233.

† *Ber.* 1878, 11, 151; 1879, 12, 1131, 1357, 1752.

‡ *Bull. Soc. chim.* 1867 [ii], 8, 7.

§ *Ibid.* 1882 [ii], 37, 410.

|| *Annalen*, 1884, 227, 283.

¶ *Ibid.* 1885, 230, 262.

** *Ibid.* 1887, 239, 34.

extremely unstable and could be isomerised very readily to terpinene; it may however be concluded that the "terebene" and "terpinylene" of Deville, Riban and Armstrong and Tilden contained appreciable quantities of terpinolene.

Owing to the ease with which terpinolene isomerises, a number of methods have been devised for its preparation in a pure state, but it is doubtful if this has ever been achieved. Recognising the readiness of its conversion into terpinene with mineral acids, Wallach and Kerckhoff* advocated the use of oxalic acid for the dehydration of α -terpineol, Baeyer† subsequently improving the method by removing the hydrocarbon in a current of steam during its formation. Later Wallach‡ used anhydrous formic acid, in place of oxalic acid and he showed that with this reagent terpinolene could be prepared also from γ -terpineol.

A completely different method of preparation was devised by Baeyer.§ By the bromination of *dipentene dihydrobromide* (I) he prepared the *tribromide*, m.p. 110° , (II), which, on treatment with zinc dust in the presence of acetic acid, gave the *acetyl* derivative (III) and this, on distillation with quinoline, gave *terpinolene* (IV).

Baeyer also prepared terpinolene by the debromination of *terpinolene tetrabromide* (V) with zinc dust in acetic acid solution at a low temperature. This latter method was improved by Semmler and Schossberger,|| who avoided the use of acetic acid, which causes isomerisation to terpinene, and carried out the debromination in ether-alcohol solution. It is possible that a hydrocarbon of greater purity might be obtained by the use of magnesium in the manner adopted by v. Braun and Lemke¶ for the preparation of pure *d*- and *l*-limonene.

Semmler and Schossberger's terpinolene is probably the purest specimen which has, up to the present, been obtained, but it would appear doubtful if it is completely homogeneous and free from terpinene. It has the following constants: b.p. $67-68^{\circ}/10$ mm., d^{20}_{400} 0.854, n_D 1.484. At the ordinary pressure, terpinolene boils at about $183-185^{\circ}$, but it cannot be distilled without considerable loss owing to polymerisation to high-boiling oils.

* *Annalen*, 1893, 275, 108.

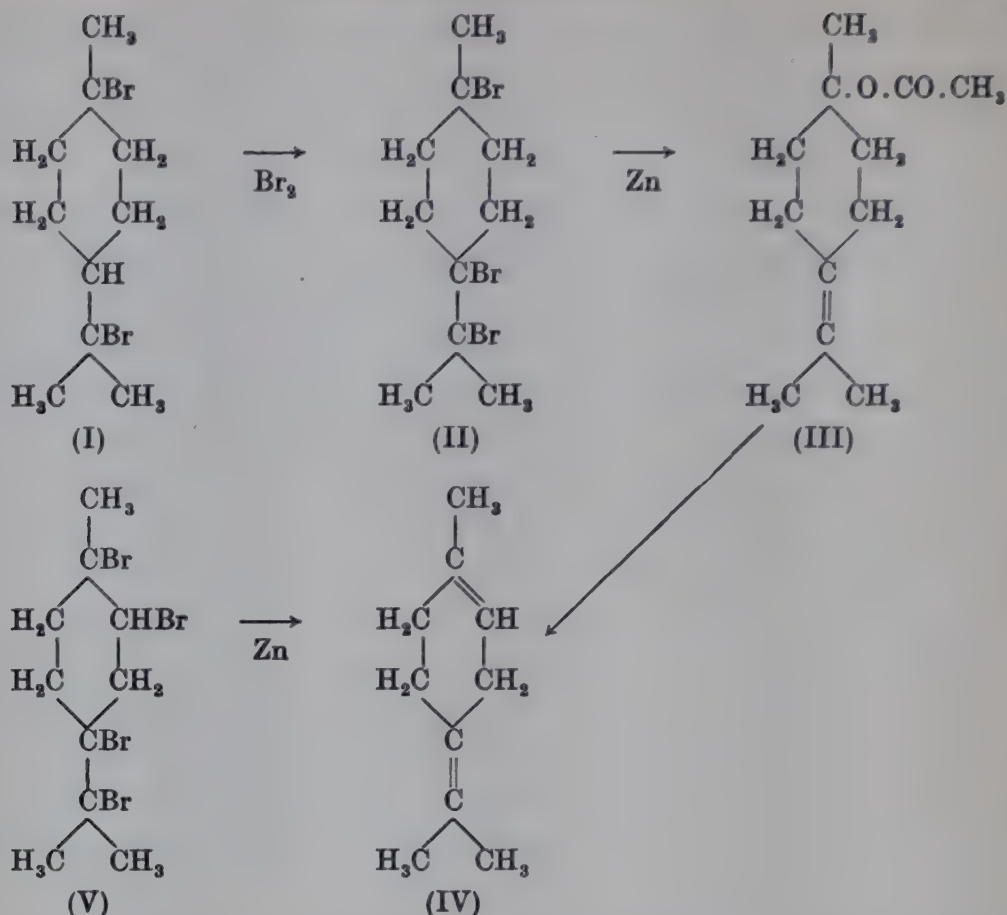
† *Ber.* 1894, 27, 448.

‡ *Annalen*, 1907, 356, 249; 1909, 368, 11.

§ *Ber.* 1894, 27, 443.

|| *Ibid.* 1909, 42, 4644.

¶ *Ibid.* 1923, 56, 1562.

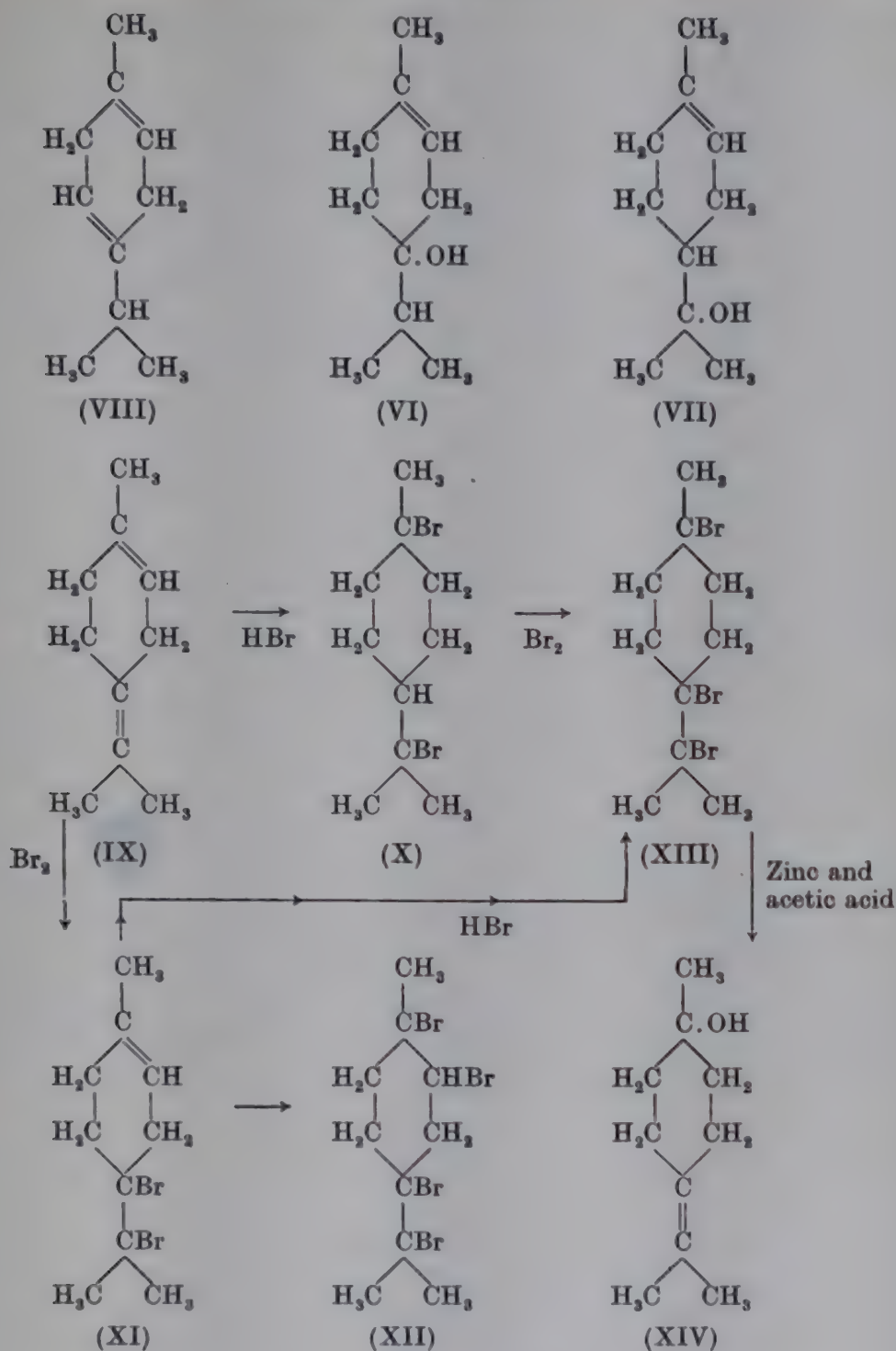


During the course of the investigations to which reference has already been made,* Baeyer established the constitution of terpinolene. Since terpinolene was formed by the dehydration of α -terpineol, which, at the time, was erroneously considered to have formula (VI) in place of that now recognised as correct (VII), Wallach[†] had suggested that terpinolene might be represented by (VIII).

Although Baeyer accepted formula (VI) for α -terpineol he did not consider that (VIII) could correctly represent terpinolene. He had observed that it was a characteristic property of olefines having an ethylenic linkage situated between two tertiary carbon atoms, as in *tetramethylethylene*, $(\text{CH}_3)_2\text{C}:\text{C}(\text{CH}_3)_2$, to give blue *nitroso*-derivatives. Now this property was shown by terpinolene, and he deduced that it must contain an ethylenic linkage of this type. Since the position of one ethylenic linkage was fixed by its formation from α -terpineol, the only possible formula for the terpene was (IX). He confirmed this by an ingenious series of

* *Ber.* 1894, 27, 443.

† *Annalen*, 1893, 277, 145.

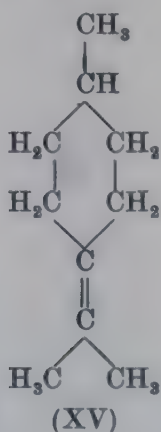


experiments. It was already known that terpinolene reacted with hydrogen bromide to give *dipentene dihydrobromide* (X), and with bromine to give a *tetrabromide* (XII). Baeyer now showed that when the hydrocarbon was treated with one molecular proportion of bromine, it gave a crystalline *dibromide* (XI), which on further bromination gave the characteristic

tetrabromide, but with hydrogen bromide gave a *tribromide* (XIII) identical with that obtained when dipentene dihydrobromide was brominated. Now when this tribromide was reduced with zinc and acetic acid, a reaction already shown by Baeyer to yield olefines if two bromine atoms occupied the 1:2 position, the *acetyl* derivative of a new terpeneol, γ -*terpineol* (XIV), was obtained. This acetyl derivative, and also the terpeneol formed on hydrolysis, gave blue nitrosochlorides and therefore undoubtedly contained the ethylenic linkage situated between two tertiary carbon atoms. Further, when the acetyl derivative was distilled with quinoline it gave terpinolene. The preparation of the hydrocarbon from the two isomeric terpeneols left no doubt that formula (IX) correctly represented its structure, and all subsequent investigations have shown it to be in strict accord with its properties.

Terpinolene has not been prepared synthetically by any direct process, but, since both α -terpineol and dipentene dihydrobromide have been synthesised (p. 150) this has been done indirectly.

The terpene cannot be reduced with sodium and alcohol or with sodamide.* When passed over palladinised asbestos at 190° in a current of carbon dioxide, Zelinski and Lewina[†] have shown that it yields a mixture of *p*-cymene and *p*-menthane. The dihydro-derivative $\Delta^{4:(8)}$ -*p*-menthene (XV) has been prepared indirectly by Semmler and Feldstein[‡] by treatment of pulegone hydrazone with sodium ethoxide.



* Lebeau and Picon, *Compt. rend.* 1914, **159**, 72.

† *Ber.* 1929, **62**, 341.

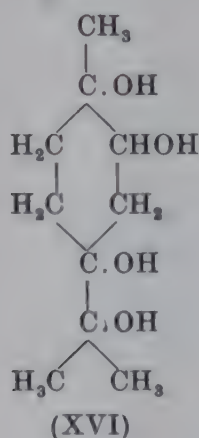
‡ *Ibid.* 1914, **47**, 387.

Unlike dipentene, terpinolene does not give a good yield of isoprene when exposed to hot metal filaments.*

Terpinolene can be very readily characterised by the preparation of its tetrabromide, 1:2:4:8-*tetrabromo-p-menthane* (XII), which was first described by Wallach.† Like the parent hydrocarbon, this derivative is somewhat unstable and its preparation is carried out best by the method devised by Baeyer,‡ who prepared it in amyl alcohol-ether solution. On allowing the ether to evaporate the bromide crystallised in plates, m.p. 118°. If only one molecular proportion of bromine was used, the dibromide, 4:8-*dibromo-Δ¹-p-menthene* (XI), was obtained, which crystallised in prisms, m.p. 69–70°. The more important reactions of these halogen derivatives have already been discussed (p. 169), but mention may be made of the observation of Wallach and Kerckhoff,§ that the tetrabromide, on treatment with alkali, yielded *p*-cymene, a reaction which originally proved the presence of the *p*-cymene nucleus in the terpene.

Although terpinolene is extremely unstable in the presence of mineral acids, being isomerised to terpinene, on treatment with the halogen acids in acetic acid solution in the cold, dipentene dihydrohalides are obtained in excellent yield.||

Terpinolene is very readily attacked by oxidising agents, but Wallach¶ found that, on cautious oxidation with potassium permanganate in ice-cold solution, it was possible to isolate the alcohol, *p-menthane-1:2:4:8-tetrol* (XVI), m.p. 148–150°.



* Staudinger and Klever, *Ber.* 1911, **44**, 2214.

† *Annalen*, 1884, **227**, 283.

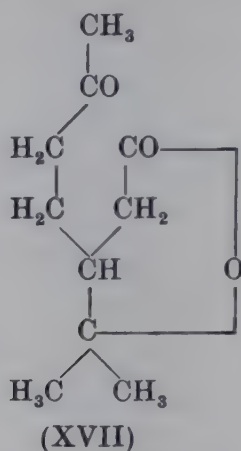
§ *Annalen*, 1893, **275**, 110.

¶ *Ibid.* 1909, **368**, 10.

‡ *Ber.* 1894, **27**, 448.

|| Wallach, *ibid.* 1887, **239**, 24.

Henry and Paget* showed that oxidation with chromic acid yields β -thujaketolactone (XVII) identical with that obtained from limonene under similar conditions (p. 156).



Oxidation of terpinolene with lead tetra-acetate gives a complex mixture of products.†

Although terpinolene contains no conjugated system, it reacts sluggishly with maleic anhydride to give an *adduct*, m.p. 182° in poor yield.‡ With maleic acid, it gives the adduct of α -terpinene, probably owing to isomerisation under the acid conditions.

The Raman spectrum of terpinolene has been investigated by Marot.§

THE TERPINENES

Under the generic name *terpinene* three hydrocarbons are recognised which yield on treatment with hydrogen chloride *terpinene dihydrochloride*, 1:4-dichloro-*p*-menthane (I),|| and are known as α -, β - and γ -terpinenes.

In 1885, shortly after the discovery of terpinolene tetra-bromide (p. 166), Wallach¶ suggested that the mixture of hydrocarbons, obtained either by the action of dilute sulphuric acid on terpin hydrate or by the inversion of pinene by the action of

* *J.C.S.* 1931, p. 25.

† Ward, *J. Amer. C.S.* 1938, **60**, 325.

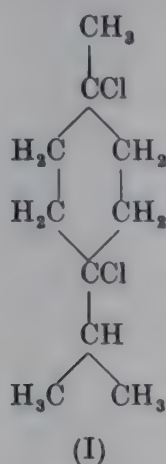
‡ Hultsch, *Ber.* 1939, **72**, 1173.

§ *Bull. Inst. Pin.* 1933 [2], pp. 38, 61.

|| The dicyclic hydrocarbons, *sabinene* and *thujene*, also yield terpinene dihydrochloride, but they can be differentiated readily from the terpinenes.

¶ *Annalen*, 1885, **230**, 260.

an alcoholic solution of sulphuric acid, contained, in addition to dipentene and terpinolene, a third hydrocarbon, which did not yield a crystalline tetrabromide.



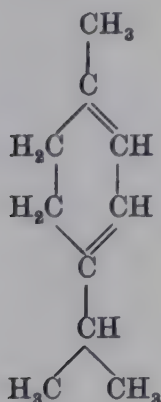
To this hydrocarbon he gave the name terpinene. Terpinene must therefore have been one of the earliest terpenes to have been prepared artificially. Two years later Wallach* found that terpinene could be characterised readily, since, on treatment with nitrous acid, it gave a crystalline *nitrosite*, m.p. 155°. With this derivative available, he was able to show that not only did terpin hydrate and pinene yield terpinene on treatment with sulphuric acid, but also that other monocyclic hydrocarbons such as dipentene and phellandrene could readily be converted into it.

The hydrocarbon fraction yielding terpinene nitrosite was at first assumed to be homogeneous, but later investigations, which will be considered in the sequel, have shown conclusively that this is not the case and that "terpinene" is a mixture. Both the naturally occurring hydrocarbon and that prepared by such reactions as those referred to above are mixtures of α - and γ -terpinenes in which either the one or the other form may predominate. The β -form does not appear to occur in nature and has only been prepared synthetically.

* *Annalen*, 1887, 239, 33.

α -TERPINENE

($\Delta^{1:3}$ -p-Menthadiene or
1-Methyl-4-isopropyl- $\Delta^{1:3}$ -cyclohexadiene)



α -Terpinene has been found to occur in nature in cardamom oil from *Elettaria Cardamomum* Maton,* in marjoram oil from *Origanum Majorana* L.† and in coriander oil from *Coriandrum sativum* L. The hydrocarbon was in no case obtained in a state of purity and its presence was only established by the isolation of the characteristic *nitrosite*, m.p. 155° , to which reference has already been made. It must be emphasised here that the name α -terpinene is reserved for the hydrocarbon giving this nitrosite.

Apart from the methods which have been devised for its synthesis (see below) a hydrocarbon fraction, of which the main constituent is α -terpinene, has been obtained in a very great variety of reactions.

The acyclic alcohols linalool‡ and geraniol§ on treatment with concentrated formic acid undergo cyclisation with formation of α -terpinene. The dicyclic hydrocarbon sabinene and the monocyclic hydrocarbons α -phellandrene and dipentene isomerise to α -terpinene on warming with dilute sulphuric acid.¶ According to Wallach,¶ α -terpinene is most conveniently prepared by treatment of α -pinene with concentrated sulphuric acid, but a more homogeneous product is probably obtained by the dehydration

* Weber, *Annalen*, 1887, **238**, 101.

† Biltz, *Ber.* 1899, **32**, 996.

‡ Bertram and Walbaum, *J. pr. Chem.* 1890 [ii], **45**, 601.

§ Bertram and Gildemeister, *ibid.* 1894 [ii], **49**, 194.

¶ Wallach, *Annalen*, 1887, **239**, 15, 44; 1893, **275**, 109; 1906, **350**, 165.

¶ *Ibid.* 1887, **239**, 35; compare Flavitzky, *Ber.* 1879, **12**, 1022; Armstrong and Tilden, *ibid.* p. 1752.

of α -terpineol with oxalic acid.* α -Terpinene is formed also when terpinene dihydrochloride is digested with either aniline, quino-line or alcoholic potassium hydroxide solution.†

Since there is no method available for obtaining the terpene free from isomerides, the constants found for α -terpinene have naturally varied. A carefully purified specimen obtained by the action of an alcoholic solution of potassium hydroxide on terpinene dihydrochloride was found by Auwers‡ to have the following constants: b.p. 180–182°, $d_4^{15^\circ}$ 0.8484, $n_D^{15.6^\circ}$ 1.4813; Richter and Wolff§ have prepared an α -terpinene by the action of aniline on terpinene dihydrochloride with the somewhat different constants, b.p. 173.5–174.8°, $d_4^{19.6^\circ}$ 0.8375, $n_D^{19.7^\circ}$ 1.477.

The determination of the constitution of α -terpinene has been difficult, since the hydrocarbon cannot be obtained in a state of purity and is always contaminated to a greater or less degree with other terpenes. In fact in 1909 Semmler|| stated, although in our opinion incorrectly, that the chemistry of the terpinenes must still be considered obscure. For the elucidation of the constitution of α -terpinene, we are mainly indebted to the prolonged investigations of Wallach and his collaborators.

In 1891 Wallach¶ showed that α -terpinene was a derivative of *p*-cymene since he found that when *dihydrocarvylamine hydrochloride* (I) was distilled or when *dihydrocarveol* (II) was digested with potassium bisulphate, a mixture of terpenes resulted from which terpinene nitrosite could be prepared in a good yield. This hydrocarbon mixture had b.p. 178–180°, d 0.847, was optically inactive and was readily converted into *p*-cymene.

Wallach suggested that α -terpinene might be represented by one of the three formulae (III), (III a), (III b), of which (III a) was unlikely since it allowed of optical activity, whereas α -terpinene was inactive. Shortly afterwards Baeyer** suggested that α -terpinene was better represented by (IV), but this must also be considered unlikely since it allows of optical activity.

* Wallach and Kerckhoff, *Annalen*, 1893, **275**, 103; compare Alder and Rickert, *Ber.* 1937, **70**, 1364.

† Wallach, *Annalen*, 1906, **350**, 148; Semmler, *Ber.* 1909, **42**, 525; Richter and Wolff, *ibid.* 1930, **63**, 1715.

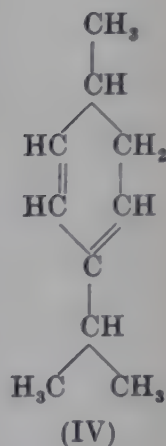
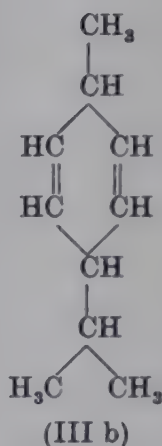
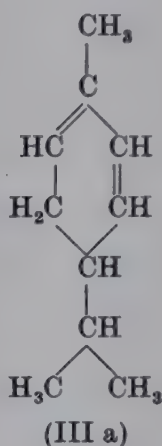
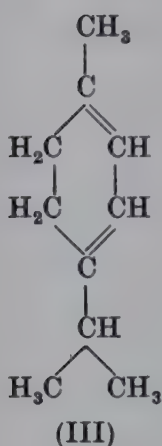
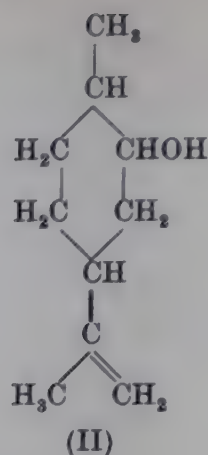
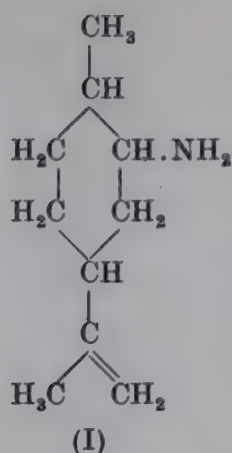
‡ *Ber.* 1909, **42**, 2428.

§ *Ibid.* 1930, **63**, 1720; compare Auwers, *ibid.* 1909, **42**, 2420.

|| *Ibid.* p. 4174.

¶ *Ibid.* 1891, **24**, 3986.

** *Ibid.* 1894, **27**, 453.



Other suggestions were made by Semmler* and by Harries,† but during the years 1906–10 Wallach‡ definitely showed that α -terpinene gave a crystalline *dihydrochloride*, m.p. 51–52°, and a crystalline *dihydrobromide*, m.p. 58–59°. These had undoubtedly been obtained previously, but, owing to their close resemblance to the corresponding derivatives of dipentene, had not been recognised. It became of fundamental importance to determine the constitution of these halogen derivatives. When the dihydrochloride was treated with an aqueous sodium hydroxide solution it was converted into the corresponding *glycol* (VIII), which differed from both the *cis*- and *trans*-forms of 1:8-*terpin* (V). In its general properties this glycol resembled the 1:8-isomeride, and the presence of two tertiary hydroxy groups was indicated by the formation of a *cineole*, which was not identical with 1:8-*cineole* (VI). Wallach§ suggested therefore that terpinene

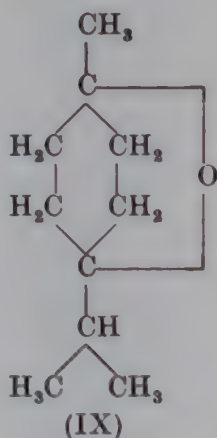
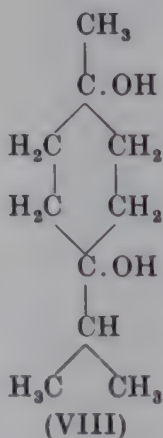
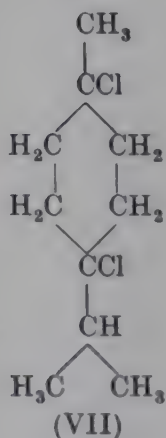
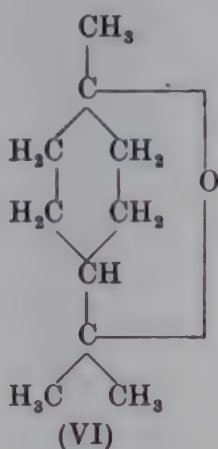
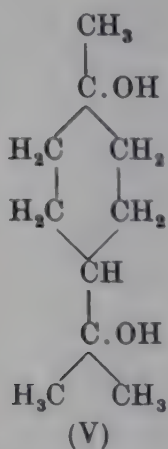
* Ber. 1901, 34, 712.

† Ibid. 1902, 35, 1169.

‡ For an excellent summary see *Annalen*, 1910, 374, 324.

§ Ibid. 1906, 350, 157; 1907, 356, 200.

dihydrochloride was represented by (VII), the terpin, *terpinene-terpin* (p-menthane-1:4-diol) by (VIII) and the corresponding cineole by (IX).



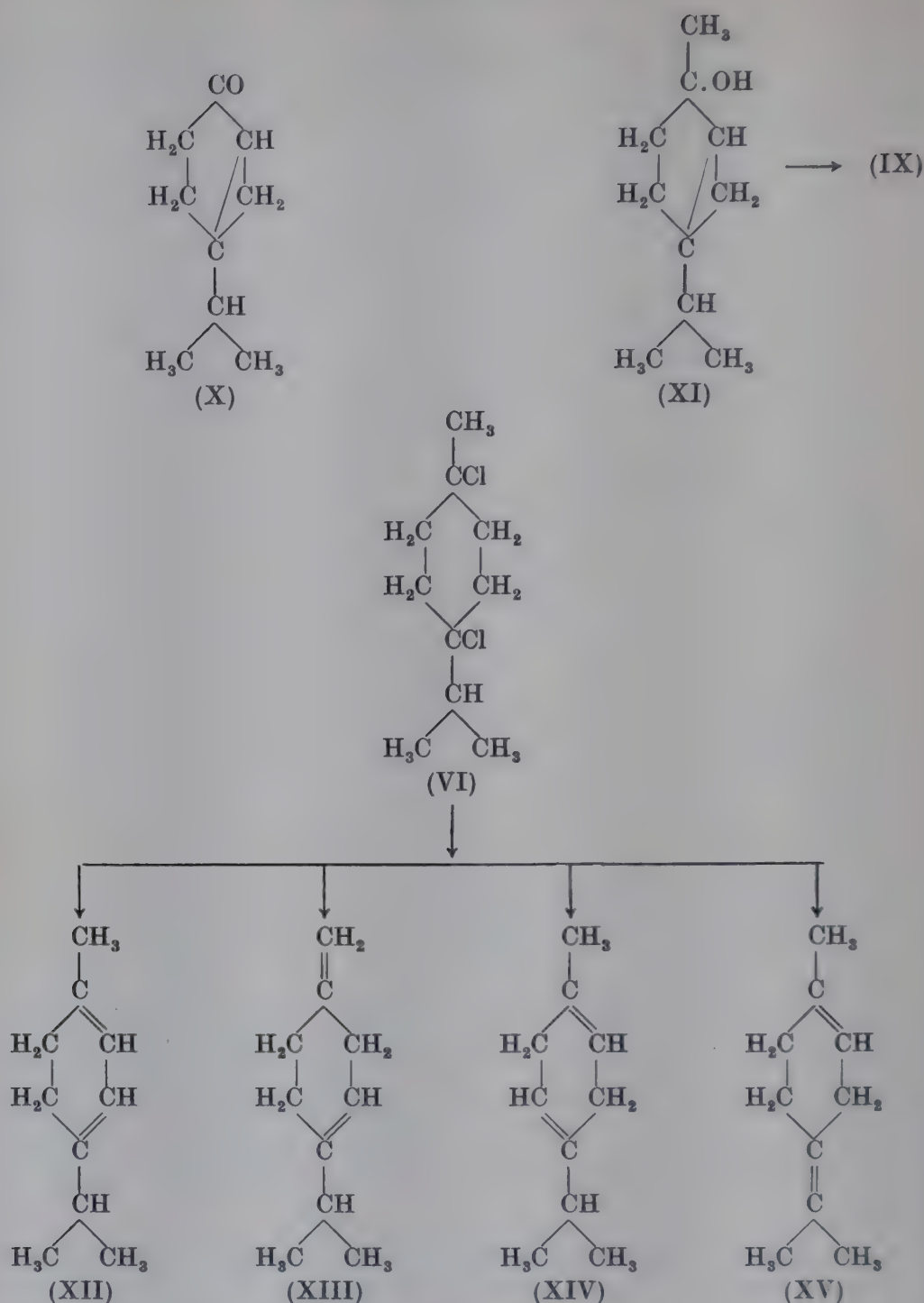
The constitution allotted to 1:4-cineole was subsequently confirmed by Wallach* by its preparation from the dicyclic ketone *sabinaketone* (X). This ketone, on treatment with the Grignard reagent, gave the *alcohol* (XI) which was isomerised with dilute sulphuric acid to the cineole, the *cyclopropane* ring undergoing fission.

Now since terpinene dihydrochloride by removal of two molecules of hydrogen chloride can be converted into α -terpinene,[†] there are four possible formulae for this hydrocarbon—(XII), (XIII), (XIV), (XV).

Of these possibilities (XV) was already eliminated, since it had been proved definitely that this was the formula of terpinolene (p. 165). α -Terpinene therefore must be represented by either formula (XII), (XIII), or (XIV).

* *Annalen*, 1906, **350**, 157; 1907, **356**, 200.

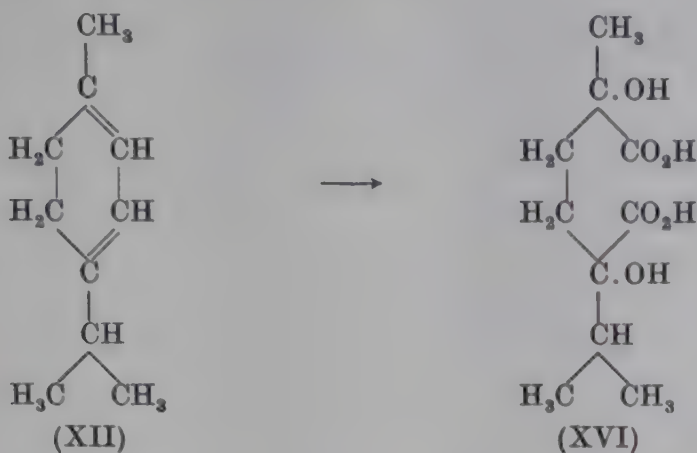
† *Ibid.* 1907, **357**, 64.



Proof that α -terpinene had formula (XII) was provided by a study of (i) its oxidation products, and (ii) the reactions of the characteristic nitrosite. On oxidation with potassium permanganate, α -terpinene gives $\alpha\delta$ -dihydroxy- α -methyl- δ -isopropyladipic acid* (XVI). The formation of this acid, the constitution of

* Wallach, *Annalen*, 1908, 362, 296; compare Henry and Paget, *J.C.S.* 1923, 123, 1878.

which has been established synthetically, leaves no doubt that α -terpinene must have formula (XII).



Now it has been shown conclusively that all specimens of α -terpinene which give a large yield of the nitrosite, give also a good yield of the substituted adipic acid on oxidation, and it follows therefore that both these are derived from the same hydrocarbon. This is confirmed by the reactions of the nitrosite, which have been studied by Wallach,* by Semmler† and by Amenomiya.‡ These investigations have shown that the nitrosite has the properties of a substance represented by formula (XVII).

Reduction with sodium and alcohol yields a mixture of *carvenone* (XVIII), *carvomenthone* (*tetrahydrocarvone*) (XIX) and *carvomenthylamine* (XX); whilst, when the *nitrolamine* (XXI) is reduced with zinc in the presence of acetic acid, the ketone (XIX) is obtained in a yield of over 60 per cent., the *oxime* (XXII) being an intermediate product.§

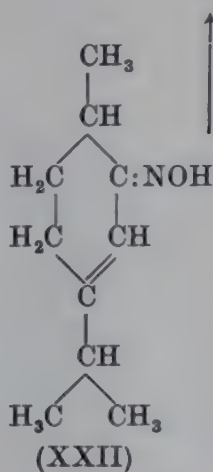
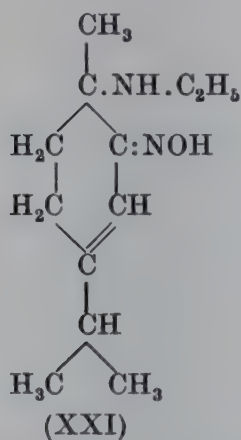
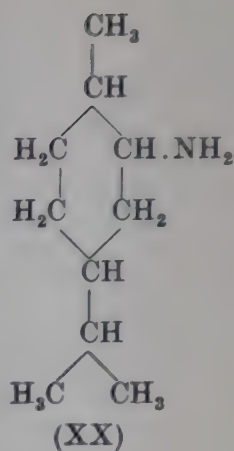
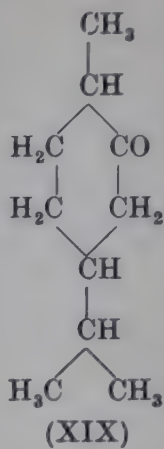
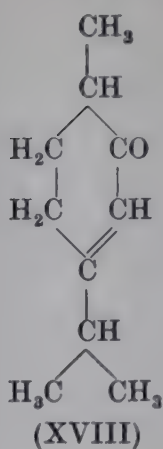
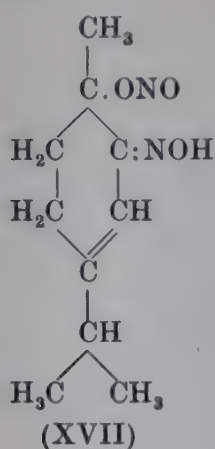
Although therefore the constitution of α -terpinene can be regarded as established, the hydrocarbon is never pure and always contains γ -terpinene (XIV) which gives a distinctive oxidation product (see p. 193). The percentage of α -terpinene present in a mixture can be estimated roughly by the yield of nitrosite, which, however, may fail to form if the percentage is low. In such cases the presence of α -terpinene can be proved by oxidation, since the substituted adipic acid can be isolated and identified very readily.

* *Annalen*, 1900, 313, 361; 1906, 350, 176; 1907, 356, 220; *Ber.* 1907, 40, 580.

† *Ber.* 1901, 34, 714.

‡ *Ibid.* 1905, 38, 2020, 2730.

§ Compare Harries, *ibid.* 1908, 41, 2524.



In addition to the methods of preparation which have been referred to, hydrocarbon mixtures consisting essentially of α -terpinene have been synthesised. Auwers and Hessenland* and, later, Auwers and Hinterseber† showed that, when the *dichloro-ketone* (XXIII) was treated with alkali, an *acid* (XXIV) was formed which, by loss of carbon dioxide, gave α -terpinene, the reactions involved being shown in the scheme given below.

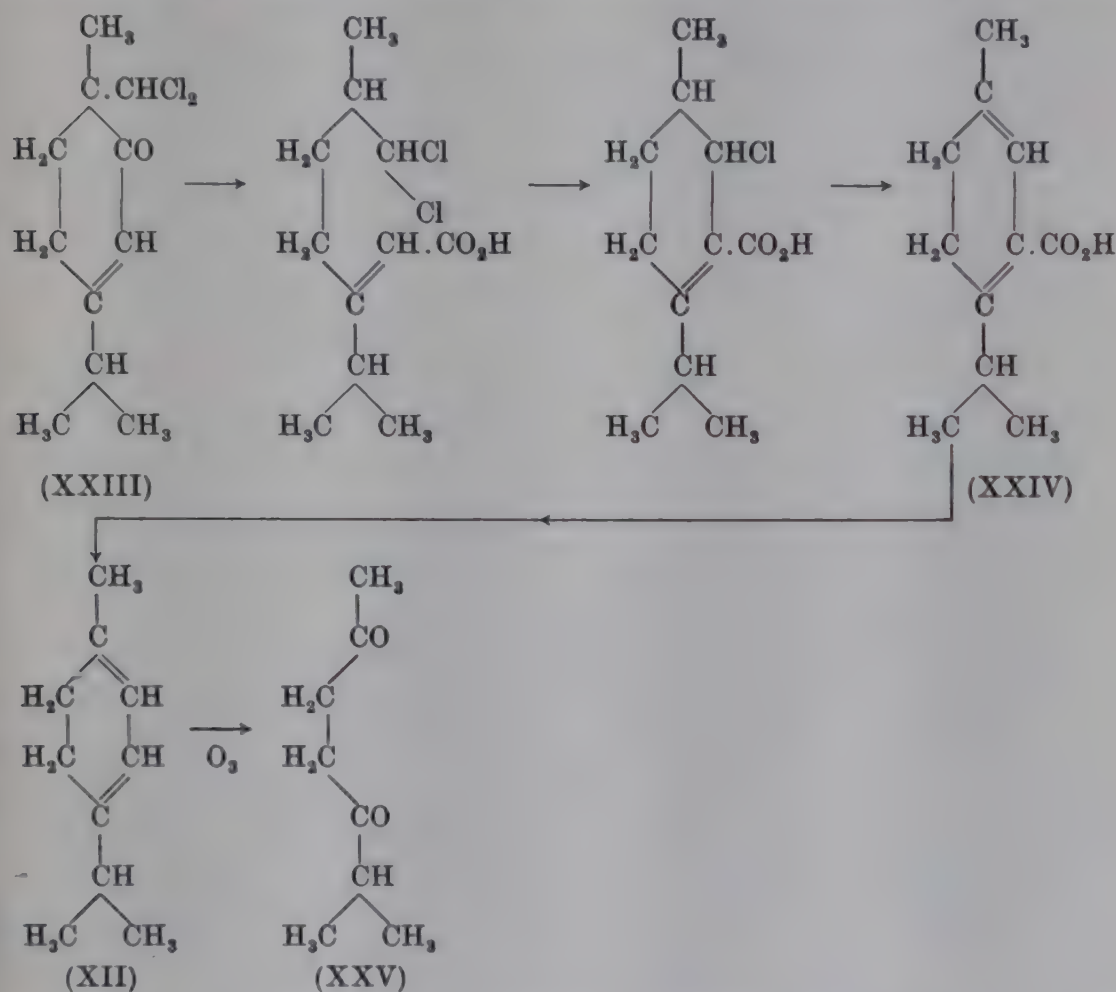
The hydrocarbon obtained in this synthesis, although probably not quite homogeneous, boiled very constantly at 65.4–66°/13.5 mm., d_4^{20} 0.834, n_D^{20} 1.4784, the molecular refraction thus showing an exaltation of 0.74, in good agreement with that shown by a number of homologues.‡ It gave an excellent yield both of the nitrosite and the substituted adipic acid, whilst, on oxidation with ozone, $\alpha\alpha$ -dimethylacetylacetonone (XXV) was obtained, a further satisfactory proof of its constitution. The constants of Auwers and Hinterseber's hydrocarbon are in very

* *Ber.* 1908, **41**, 1790.

† *Ibid.* 1915, **48**, 1357.

‡ Compare Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], **82**, 107.

close agreement with the values quoted by Richter and Wolff (p. 175) for a carefully purified specimen of α -terpinene obtained from terpinene dihydrochloride. It is probable that these are the purest specimens of α -terpinene which have been prepared.



Another method of synthesis was devised by Harries and Majima,* who obtained the hydrocarbon by the distillation (under diminished pressure) of the phosphate of 2-amino- Δ^3 -p-menthene (XXVI). This hydrocarbon also consisted essentially of α -terpinene, although an examination of the products which were formed on oxidation showed γ -terpinene to be present also.† It had the constants: b.p. $68-70^\circ/15$ mm., $d_4^{18^\circ} 0.8453$, $n_D^{18^\circ} 1.4858$.

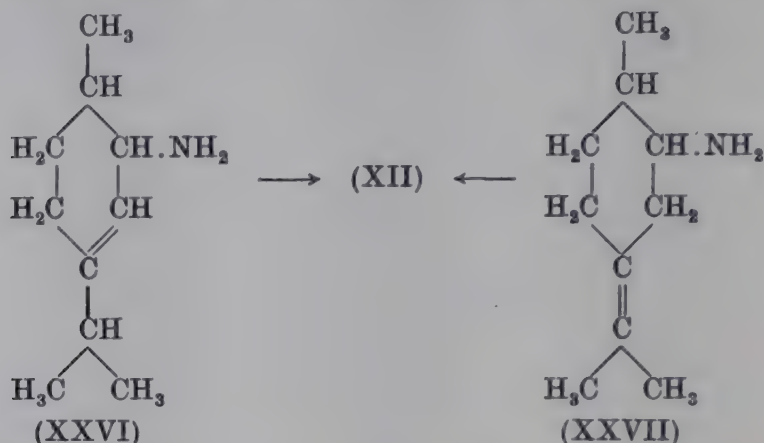
Harries and Morrell‡ have synthesised α -terpinene by a somewhat similar method, namely by the distillation of the phosphate of 2-amino- $\Delta^{4(8)}$ -p-menthane (XXVII). The position of the ethy-

* Ber. 1908, 41, 2521.

† Ibid. 1915, 410, 71.

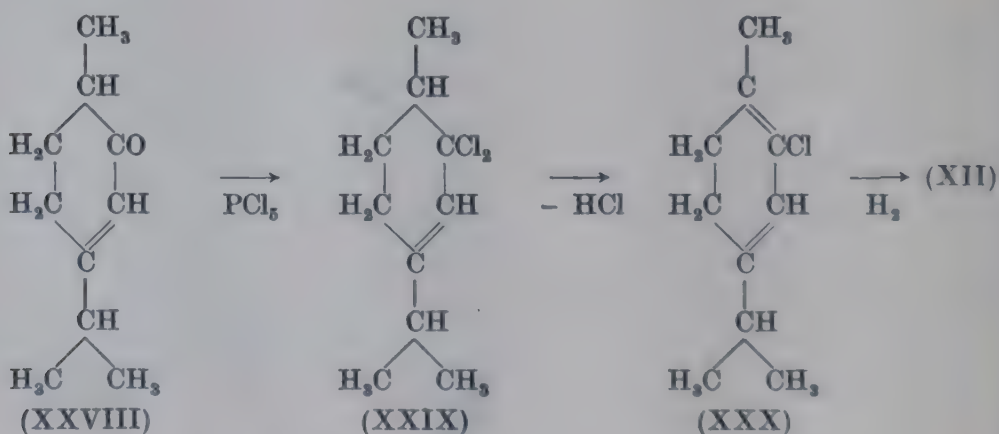
‡ Wallach, Annalen, 1909, 368, 15.

lenic linkage in the amine had been proved previously by Morrell* and a shifting of the exocyclic linkage evidently occurs



during the reaction. The α -terpinene (b.p. $60\text{--}63^\circ/12\text{ mm.}$, $d_{18.5}^{18.5} 0.8474$, $n_D^{18.5} 1.4872$, $[R_L]_D = 46.19$) was not pure since, after removal of the α -terpinene as the nitrosite, a second hydrocarbon was separated, b.p. $63\text{--}65^\circ/14\text{ mm.}$, $d_{19}^{19} 0.8466$, $n_D^{19} 1.4903$, which, however, was not identified.

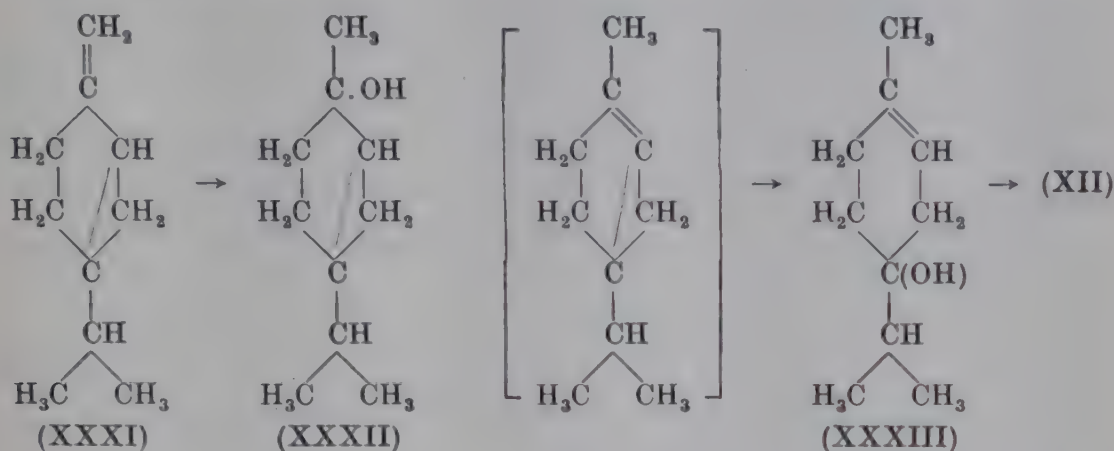
A synthesis of α -terpinene was carried out by Semmler,[†] starting from *carvenone* (XXVIII). This ketone on treatment with phosphorus pentachloride gave 2-chloro- $\Delta^{1:3}$ -p-menthadiene (XXX) by loss of hydrogen chloride from the primary product (XXIX). When the chloride was reduced with sodium and alcohol below 50° α -terpinene was obtained. The hydrocarbon, b.p. $61.5\text{--}62.5^\circ/10\text{ mm.}$, $d^{20} 0.845$, $n_D^{20} 1.4905$, was fairly homogeneous and gave an excellent yield of the substituted adipic acid on oxidation.



* *Ber.* 1911, **44**, 2560.

† *Ibid.* 1908, **41**, 4474.

Mention may finally be made of the synthesis* of α -terpinene from sabinene (XXXI) by the action of dilute sulphuric acid, the alcohols (XXXII) and (XXXIII) being intermediate stages in the reaction.



α -Terpinene is a colourless oil having a pleasant odour of lemons. It can be distilled without decomposition at the ordinary pressure, but resinifies somewhat readily when kept. The absorption spectrum in the ultra-violet has been studied by Crymble, Stewart, Wright and Rea[†] and has been compared with that of limonene and terpinolene. A characteristic property of α -terpinene, which distinguishes it from γ -terpinene, dipentene and other hydrocarbons, was first observed by Baeyer.[‡] When shaken with Beckmann's chromic acid reagent it is immediately oxidised with the separation of brown resinous flakes (see below). The *nitrosite*, m.p. 155° , is best prepared by the addition of acetic acid to a solution of the terpene in light petroleum, to which an aqueous solution of sodium nitrite has been added. The *benzoyl* derivative of the nitrosite melts at $77-78^{\circ}$ whilst, by treatment with bases, a large number of *nitrolamines* have been prepared, for details of which reference may be made to the original papers.[§]

α -Terpinene does not give either a crystalline di- or tetrabromide, but with the halogen acids crystalline derivatives are readily obtained.^{||} The *dihydrochloride* melts at $51-52^{\circ}$, the *dihydrobromide* at $58-59^{\circ}$ and the *dihydroiodide* at 76° , melting-

* Wallach, *Annalen*, 1917, **414**, 199.

[†] *J.C.S.* 1911, **99**, 1267; compare Auwers, *Ber.* 1911, **44**, 3538; see also p. 186.

[‡] *Ber.* 1894, **27**, 815; compare Richter and Wolff, *ibid.* 1927, **60**, 477.

[§] *Inter al.*, Wallach, *Annalen*, 1887, **241**, 316; 1889, **252**, 133.

^{||} Wallach, *ibid.* 1906, **350**, 145; 1907, **356**, 198.

points which are all somewhat higher than those of the corresponding derivatives of dipentene. According to Wallach,* in carbon disulphide solution a *monohydrochloride*, b.p. 85–95°/11 mm., can be prepared. The conversion of the dihydrochloride into terpinene-terpin has already been referred to on p. 176.†

Although, as has been shown by Semmler,‡ some conversion into terpinolene does take place in the presence of an alcoholic solution of sulphuric acid, α -terpinene shows little tendency to isomerise to other terpenes and even prolonged treatment with phosphoric acid leaves it unaffected.§ In agreement with this is the observation of Staudinger and Klever|| that the terpene does not pass readily into isoprene in the presence of hot metal filaments. When heated with sulphur *p*-cymene is obtained in a yield of about 50 per cent.,¶ whilst Fuller's earth causes polymerisation to high boiling products.**

Sabatier and Senderens†† have shown that reduction with hydrogen in the presence of nickel yields *p*-menthane, whereas Semmler‡‡ found repeated reduction with sodium and amyl alcohol gave Δ^2 -*p*-menthene. Zelinski and Lewina§§ have distilled the hydrocarbon over palladinised asbestos in a current of carbon dioxide, when a mixture of *p*-menthane and *p*-cymene is formed. The same mixture of hydrocarbons is formed when the terpene is shaken in an admixture of nitrogen with palladium, which has been saturated previously with hydrogen.||||

Reference has already been made to the oxidation of α -terpinene with ozone and potassium permanganate; the action of chromyl chloride on the terpene has been studied by Henderson and Cameron,¶¶ who have found that *p*-tolyl propaldehyde; $\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}(\text{CH}_3) \cdot \text{CHO}$, and *p*-tolyl methyl ketone, $\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{CH}_3$, are formed. Since these products result from the oxidation of *p*-cymene with this reagent, it is probable that conversion into *p*-cymene precedes oxidation.

* *Annalen*, 1906, 350, 145; 1907, 356, 198.

† See also p. 303.

‡ *Ber.* 1909, 42, 965.

§ Carter, Smith and Read, *J.S.C.I.* 1925, 44, 546 T.

|| *Ber.* 1911, 44, 2214.

¶ Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 356.

** Venable, *J. Amer. C.S.* 1923, 45, 733.

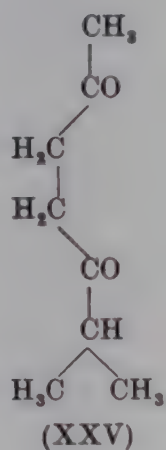
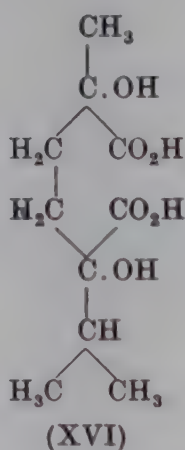
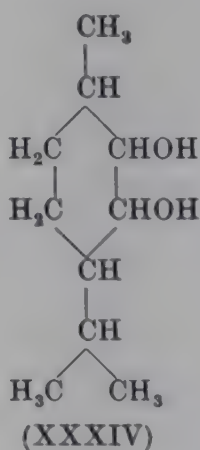
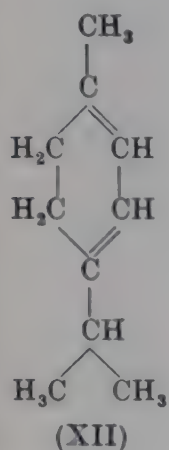
†† *Compt. rend.* 1901, 132, 1254.

‡‡ *Ibid.* 1929, 62, 341.

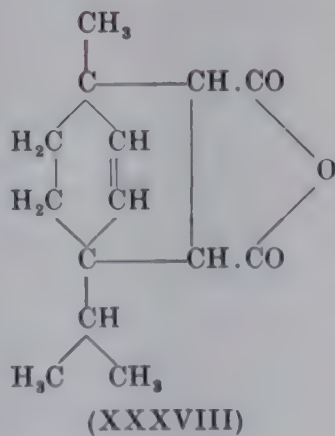
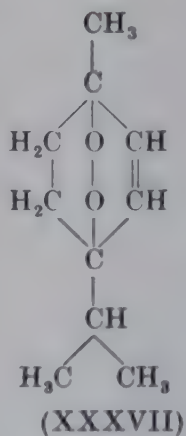
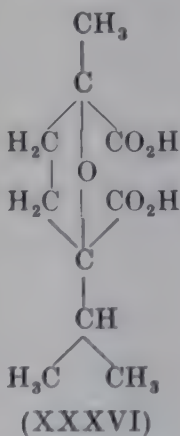
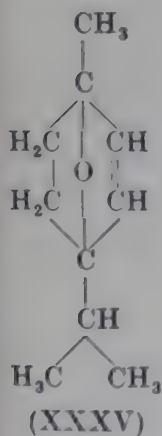
§§ *Richter and Wolff, Ber.* 1930, 63, 1721.

¶¶ *J.C.S.* 1909, 95, 969.

The oxidation of α -terpinene with Beckmann's chromic acid mixture has been investigated by Paget and Henry,* although the ease with which the hydrocarbon was attacked by this reagent was noted by Baeyer many years ago (compare p. 183). The main product formed is *dimethylacetonylacetone* (XXV), only a very small amount of the substituted adipic acid (XVI) being obtained. It would appear to be probable that the first product of the reaction is the *glycol* (XXXIV), which would account for the small yield of the acid.



Elson, Gibson and Simonsen† have found that when α -terpinene is oxidised with perbenzoic acid in chloroform solution 1:4-oxido- Δ^2 -p-menthene (XXXV), b.p. 115–117°/50 mm., d_{21}^{21} 0.9281, n_D^{21} 1.4728, is formed. The constitution of this oxide was established by its oxidation with potassium permanganate to 1:4-cineolic acid (XXXVI).



* J.C.S. 1921, 119, 1714; 1923, 123, 1878.

† Ibid. 1929, p. 2732; compare Richter and Wolff, Ber. 1930, 63, 1720.

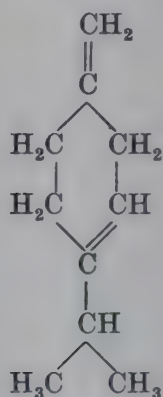
Irradiation of α -terpineol in the presence of oxygen and a fluorescent dye yields *ascaridole* (XXXVII)* (see p. 446).

Oxidation of α -terpinene with lead tetra-acetate gives a complex mixture of products;† its auto-oxidation has been studied by Bodendorf.‡

Booker, Evans and Gillam§ have confirmed the presence of a conjugated system in α -terpinene by an examination of the absorption spectrum. Furthermore, the hydrocarbon reacts readily with maleic anhydride to give the *adduct* (XXXVIII), m.p. 60–61°.||

β -TERPINENE

($\Delta^{1(7):3}$ -p-Menthadiene or
1-Methylene-4-isopropyl- Δ^3 -cyclohexene)



Up to the present β -terpinene has not been found to occur in nature. It has been prepared synthetically by Wallach¶ from *sabinene* (I). When *sabinene* is oxidised with potassium permanganate in alkaline solution *sabinenic acid* (II) is obtained, which, on further oxidation with the same reagent in acid solution, yields the dicyclic ketone *sabinaketone* (III). By the condensation of this ketone with ethyl bromoacetate in the presence of zinc a *hydroxy-ester* (IV) is formed, the *cyclopropane* ring iso-

* Schenck and Ziegler, *Naturwiss.* 1944, **32**, 157.

† Ward, *J. Amer. C.S.* 1938, **60**, 325.

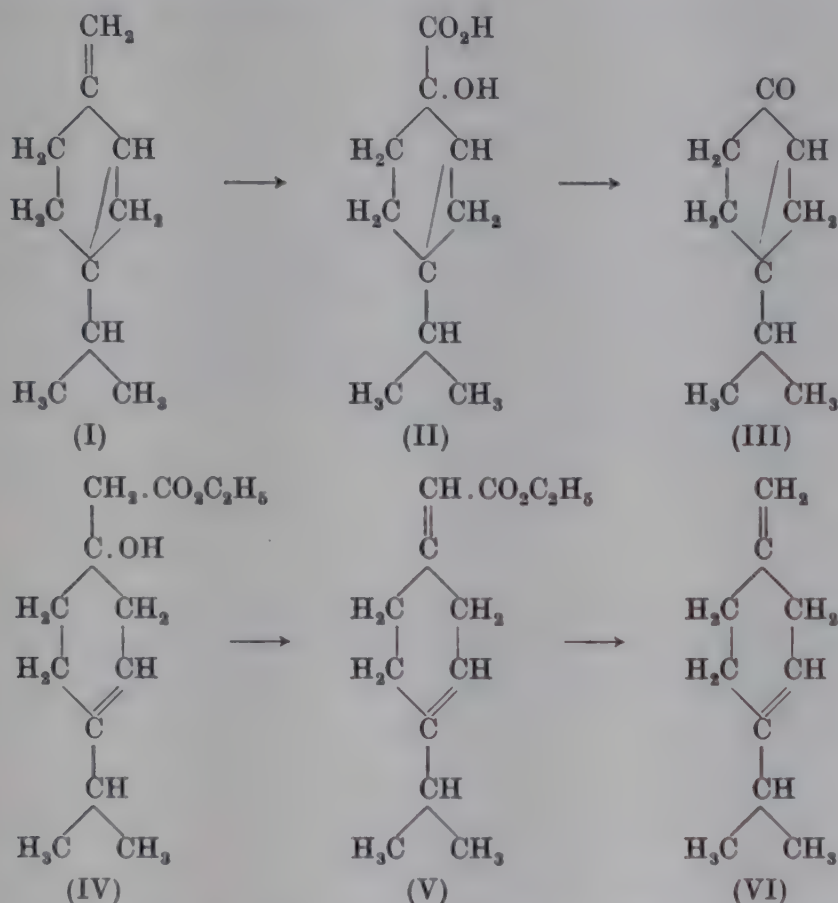
‡ *Arch. Pharm.* 1933, **271**, 1.

§ *J.C.S.* 1940, p. 1453.

|| Goodway and West, *J.C.S.* 1940, p. 702; West, *ibid.* 1941, p. 140; Gascoigne, *J. Proc. Roy. Soc. New South Wales*, 1940, **74**, 353; compare Littmann, *J. Amer. C.S.* 1935, **57**, 586; Diels, Koch and Frost, *Ber.* 1938, **71**, 1163; Alder, *ibid.* p. 2210; Hultsch, *ibid.* 1939, **72**, 1173.

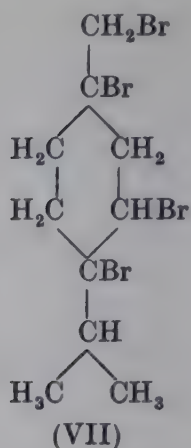
¶ *Annalen*, 1907, **357**, 69; 1908, **362**, 288.

merising. When the hydroxy-ester is heated with acetic anhydride it loses water, giving the *unsaturated ester* (V). This ester on hydrolysis yields the corresponding *acid* which, when slowly distilled at the ordinary pressure, loses carbon dioxide with formation of β -terpinene (VI).



β -Terpinene is an oil, b.p. $173\text{--}174^\circ$, d^{22}_D 0.838, n^{22}_D 1.4754. As is to be anticipated from its constitution, the molecular refraction (obs. 45.72, calc. 45.24) shows a marked exaltation.* β -Terpinene differs from both α - and γ -terpinenes in yielding a crystalline *tetrabromide* which must be represented by formula (VII). It is formed when bromine is added to a well-cooled ether-alcohol solution of the terpene and crystallises from ethyl acetate in prisms, m.p. $154\text{--}155^\circ$. With hydrogen chloride β -terpinene yields terpinene dihydrochloride, whilst with nitrous acid on long standing some α -terpinene nitrosite is formed, which indicates that in the presence of acids β -terpinene slowly isomerises to α -terpinene.

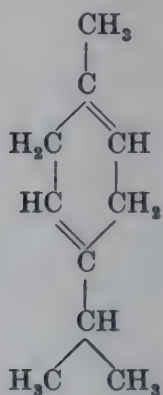
* Compare Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], 82, 108.



β -Terpinene is very readily oxidised, and on exposure to the air, especially in the presence of sunlight, dihydrocuminaldehyde and cuminaldehyde are formed. The products obtained on oxidation with potassium permanganate have only been subjected to a preliminary examination.*

γ -TERPINENE

($\Delta^{1:4}$ -p-Menthadiene or
1-Methyl-4-isopropyl- $\Delta^{1:4}$ -cyclohexadiene)



Although it has long been known that "terpinene" prepared by any of the methods mentioned on p. 173 contained γ -terpinene its occurrence in nature has only been established comparatively recently.

It was shown by Walbaum and Müller[†] to occur in coriander oil from *Coriandrum sativum* L., in lemon oil from *Citrus Medica* L. and by Gildemeister and Müller[‡] in cumin oil from *Cuminum*

* Wallach, *Annalen*, 1908, 362, 292.

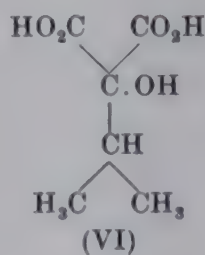
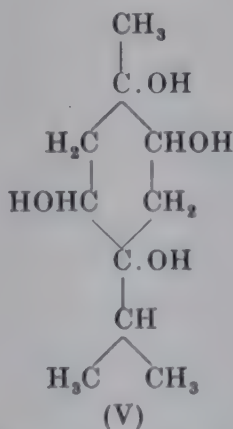
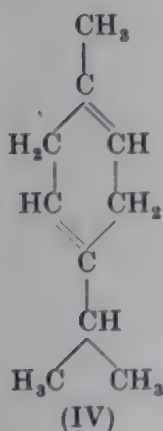
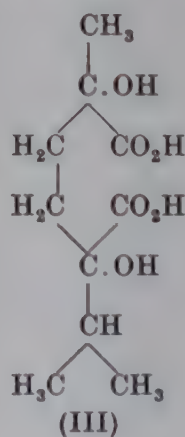
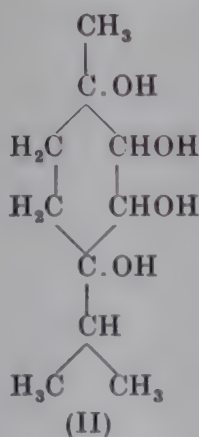
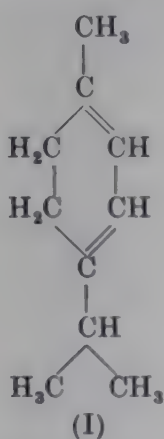
† Wallach *Festschrift*, 1909, p. 660.

‡ *Ibid.* pp. 443, 448.

Cyminum L. It is present also, probably free from admixture with α -terpinene, in Ajowan oil* from *Carum copticum* Benth. et Hook. f., in oil of samphire from *Crithmum maritimum* L. and in the oils from *Mosla japonica* and *M. grosseserrata*.† The recognition that the terpene present in the three latter oils was γ -terpinene is of especial interest and is further discussed below. A small amount is present also in the oil from *Cupressus macrocarpa*.‡

As already mentioned (p. 173) "terpinene" was for some time considered to be homogeneous, but this was found to be incorrect when Wallach§ observed that on oxidising the hydrocarbon with potassium permanganate, in addition to $\alpha\delta$ -dihydroxy- α -methyl- δ -isopropyl adipic acid (III), a tetrahydroxy-*p*-menthane, m.p. 237° , was formed.

This alcohol could not be derived from α -terpinene (I) and be represented by (II), since, on further oxidation it did not give



* Schimmel's Report, 1909, Oct., p. 15.

† Richter and Wolff, Ber. 1927, 60, 477.

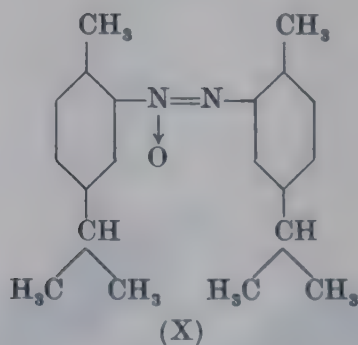
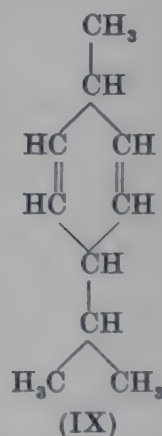
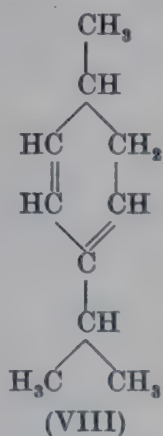
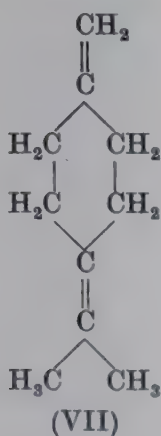
‡ Briggs and Sutherland, J. Org. Chem. 1942, 7, 397.

§ Annalen, 1908, 362, 297.

the substituted adipic acid (III). Wallach concluded, therefore, that it must have formula (V) and be *p*-menthane-1:2:4:5-tetrol, resulting from the oxidation of γ -terpinene (IV). The constitution assigned by Wallach to the alcohol was confirmed by the subsequent experiments of Gildemeister and Müller, who showed that it gave, on further oxidation with potassium permanganate, *isopropyl tartronic acid* (VI) and oxalic acid.

Although the presence of γ -terpinene in "terpinene" was thus established, the percentage present was small, the main constituent being the α -isomeride; further, no crystalline derivatives had been prepared.

In 1913 Francesconi and Sernagiotto* separated from Italian oil of samphire an optically active terpene, b.p. 178–180°. This yielded terpinene dihydrochloride and also a crystalline *nitrosochloride*, the α -form of which had m.p. 101–102° and the β -m.p. 103–104°. Both these nitrosochlorides gave on treatment with alkali a yellow substance, m.p. 53°. Francesconi and Sernagiotto gave this terpene, which they considered to be new, the name *crithmene* and the structure (VII).



* *Gazzetta*, 1913, 43, I, 608, II, 66.

The same hydrocarbon was separated some years later by Delépine and de Belsunge* from French oil of samphire and studied by Longuet.† In 1921 Murayama‡ isolated from the essential oils derived from *Mosla japonica* Maxim, *M. grosse-serrata* Maxim and from Ajowan oil a terpene, b.p. 173–175°, to which he gave the name *moslene*. He prepared from this a *nitrosochloride*, m.p. 111°, and a *nitrosate*, m.p. 116°, and he showed that the nitrosochloride of moslene, like that of crithmene, gave on treatment with alkali a yellow substance, m.p. 52–53°, which he identified as the *azoxy* compound (X). Murayama did not regard moslene as identical with crithmene and he suggested that its constitution was most probably represented either by formula (VIII) or (IX).

Richter and Wolff§ have shown conclusively that both crithmene and moslene are identical with γ -terpinene. The hydrocarbon prepared by these authors had b.p. 69–73°/20 mm., $d_{16}^{16^\circ}$ 0.8515, $n_D^{18^\circ}$ 1.4785, $\alpha_D + 2.5^\circ$, and gave a nitrosochloride, m.p. 111°, which was converted by sodium ethoxide into the azoxy body, m.p. 52–53° (X). The identity with γ -terpinene was proved by its oxidation to *p-menthane-1:2:4:5-tetrol* (V) and by its conversion into terpinene dihydrochloride. The γ -terpinene from oil of samphire is evidently very nearly pure, although the observed optical activity shows the presence of some impurity.

In the same communication Richter and Wolff showed that the terpene fraction from Ajowan oil known as “thymene”, which had already been proved by Gildemeister and Müller|| to be γ -terpinene, gave the crystalline nitrosochloride, m.p. 111°, mentioned above. This body may therefore now be considered definitely to be derived from γ -terpinene and its non-formation from the “synthetic” γ -terpinenes is probably due to the presence of impurities. By careful fractional distillation of “thymene” Richter and Wolff have prepared pure γ -terpinene. It boils at 183°/760 mm., $d_4^{15^\circ}$ 0.853, $n_D^{15.6^\circ}$ 1.4754 and its calorific value is 1472.4 k. cal. per molecule.

Birch¶ has obtained γ -terpinene by the reduction of *p*-cymene in liquid ammonia with sodium and alcohol. This constitutes a

* Bull. Soc. chim. 1918 [iv], 23, 34.

† J. Pharm. Soc. Japan, 1921, p. 769.

|| Wallach Festschrift, 1909, pp. 443, 448.

† Bull. Sci. Pharmacol. 1925, 32, 65.

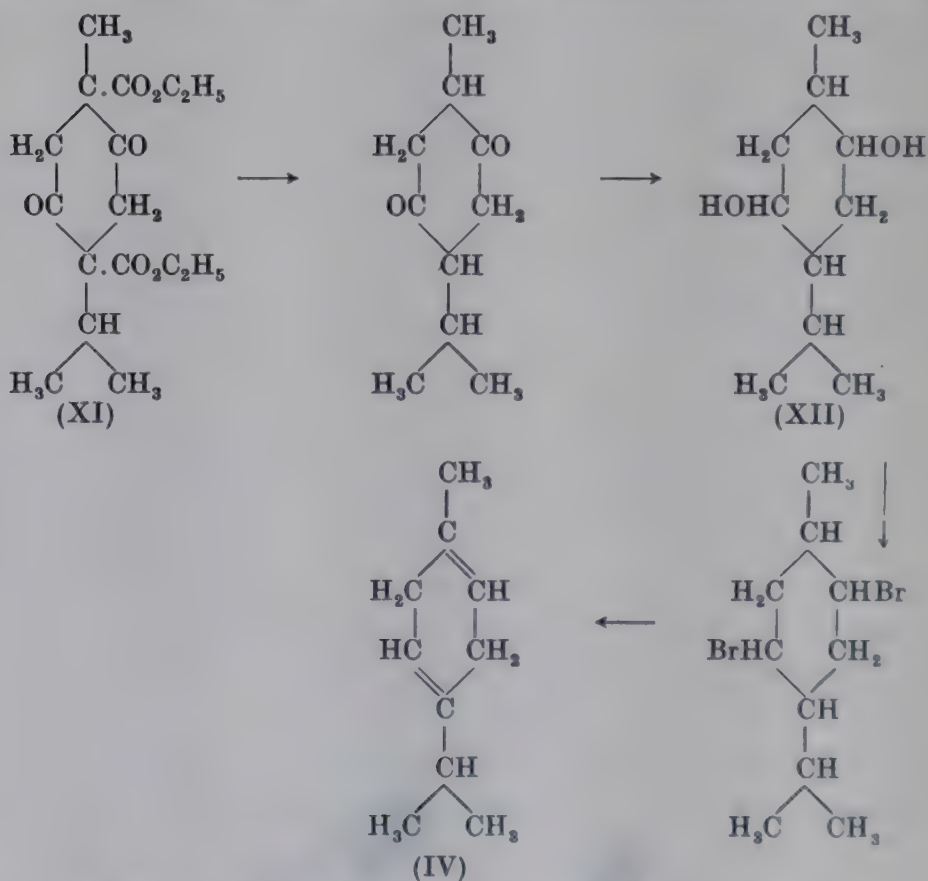
§ Ber. 1927, 60, 477; 1930, 63, 1714.

¶ J.C.S. 1944, p. 432.

synthesis of the hydrocarbon. In 1893 Baeyer* prepared from ethyl 1-methyl-4-isopropylcyclohexane-2:5-dione-1:4-dicarboxylate (XI), by the reactions shown schematically below, a hydrocarbon, b.p. 174° , which probably consisted essentially of γ -terpinene.

Baeyer apparently did not purify the *p*-menthane-2:5-diol (XII), which was prepared subsequently by Henderson and Sutherland† by the reduction of thymoquinol by the Sabatier-Senderens process. By the elimination of water with potassium hydrogen sulphate these authors obtained a hydrocarbon, b.p. $179^{\circ}/760$ mm., n_D^{20} 1.4779, which possibly also consisted mainly of γ -terpinene, but, owing to the limited quantity available, they were not able to characterise it. A renewed investigation of this synthetic hydrocarbon would be of considerable interest.

γ -Terpinene yields a crystalline *tetrabromide*, m.p. 128° , whilst with the halogen acids the terpinene dihalides are obtained. As has been pointed out by Richter and Wolff, unlike α -terpinene, γ -terpinene is only slowly attacked by Beckmann's chromic acid



* *Ber.* 1893, **26**, 232; compare Harries, *ibid.* 1902, **35**, 1170.

† *J.C.S.* 1910, **97**, 1616.

reagent. In the presence of other terpenes it can be identified most readily by oxidation to the erythritol, m.p. 237° , but when present in quantity the preparation of either the nitrosochloride or the nitrosate would probably prove more convenient.

γ -Terpinene is very readily oxidised on exposure to the air with liberation of hydrogen peroxide, and if it is shaken with oxygen in the presence of osmium *p*-cymene is formed in a yield of over 70 per cent. It is decomposed also when kept in contact with palladium which has been previously saturated with hydrogen, a mixture of *p*-menthane and *p*-cymene being obtained.*

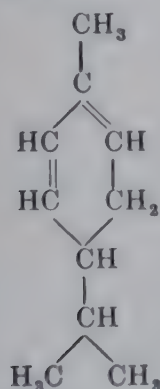
The Raman spectrum of γ -terpinene has been studied by Marot.†

THE PHELLANDRENES

The phellandrenes, α - and β -phellandrene, have long been known, although it was many years after their discovery that the exhaustive investigations of Wallach elucidated the difficult problem of their constitution and their relationship to one another. Owing to the close resemblance in properties shown by the derivatives of these two terpenes, it is now impossible, in the case of the earlier investigations, to determine which isomeride was actually isolated. Fortunately the chemistry of the two hydrocarbons is now sufficiently clear for them to be discussed separately.

α -PHELLANDRENE

($\Delta^{1:5}$ -*p*-Menthadiene or
1-Methyl-4-isopropyl- $\Delta^{1:5}$ -cyclohexadiene)



* Richter and Wolff, *Ber.* 1930, **63**, 1718.

† *Bull. Inst. Pin*, 1933 [ii], pp. 38, 61.

In 1842 Cahours* isolated from the oil of bitter fennel (*Foeniculum vulgare*) a hydrocarbon, which he recognised as having a different density from the hydrocarbons obtained from turpentine and lemon oils. He also found that on treatment with oxides of nitrogen it gave a crystalline substance. The composition of this body, *phellandrene nitrosite*, which later played a considerable part in the identification of the hydrocarbon, was not determined by Cahours or by Chiozza, who examined it somewhat later. In 1869 Bunge† assigned to the nitrosite the formula $C_{10}H_{15}O_3N_2$, but it remained for Pesci‡ to show that the correct formula was $C_{10}H_{16}O_3N_2$. Pesci obtained his hydrocarbon, for which he suggested the name *phellandrene*, from the oil of the water fennel (*Phellandrium aquaticum*) and in the course of his investigations he made a number of important observations, all of which received subsequent confirmation in the work of Wallach and his collaborators.

In his first publication on this subject Wallach§ considered Cahours' and Pesci's hydrocarbons to be identical, and he|| later separated *l*-phellandrene from the oil derived from *Eucalyptus amygdalina* and *d*-phellandrene from oil of elemi. Various observations had, however, made doubtful the identity and homogeneity of the nitrosites prepared from these hydrocarbons, more especially since the optical rotatory powers showed great variations.¶ In 1901 Schreiner** showed that the phellandrene nitrosite prepared from the phellandrene derived from eucalyptus oil could be separated into two nitrosites, one of which had m.p. 120–121° and $[\alpha]_D + 123.5^\circ$ (in chloroform) and the other m.p. 105–106° and $[\alpha]_D - 36^\circ$.

In a series of communications published during the years 1902–4 Wallach†† showed that there were *two* phellandrenes which he designated as α -phellandrene and β -phellandrene. The phellandrene from bitter fennel oil and from elemi oil was *d*- α -phellandrene, whilst its optical enantiomorph, *l*- α -phellandrene, occurred in eucalyptus oil. On the other hand, the phellandrene

* *Ann. chim.* 1841 [iii], 2, 305.

† *Z. für Chem.* 1869, p. 579.

‡ *Jahresbericht*, 1883, p. 1424; 1884, p. 547; 1885, p. 698.

§ *Annalen*, 1887, 239, 40.

|| *Ibid.* 1888, 246, 232, 282; 1889, 252, 102; 1895, 287, 371.

¶ Compare Gildemeister and Stephan, *Arch. Pharm.* 1897, 235, 591.

** *Pharm. Arch.* 1901, 4, 90.

†† *Annalen*, 1902, 324, 270; 1904, 336, 9.

from water fennel oil was structurally different from α -phellandrene and was called β -phellandrene. The recognition of this difference in constitution led shortly afterwards to a determination of the structure of the two hydrocarbons.

d- α -Phellandrene has been shown to occur in ginger grass oil, star aniseed oil,* Ceylon and Seychelles oil of cinnamon and in very small quantities in the oil from the gum-oleo-resin of *Boswellia serrata*,† whilst the *l*-hydrocarbon occurs in quantity in various eucalyptus oils (*E. dives*, *E. phellandra*). The majority of the investigations on the constitution of the terpene have been made with oil derived from the latter sources.

α -Phellandrene is a colourless mobile oil which, owing to its tendency to decompose when distilled at the ordinary pressure, is somewhat difficult to obtain quite pure. The laevorotatory form has b.p. 58–59°/16 mm.,‡ d_4^{20} 0.8324, n_D^{20} 1.4724, $[\alpha]_D^{20}$ –177.4°.§ The dextrorotatory form would not appear to have been obtained in an equal state of purity, since the highest recorded rotation|| is $[\alpha]_D + 45^\circ$. When distilled at the ordinary pressure the terpene boils at about 175–176°. The molecular refraction of the hydrocarbon shows little exaltation (obs. 45.65, calc. 45.24), a result which, as pointed out by Auwers and Eisenlohr,¶ is in good agreement with the accepted constitution.

The constitution of α -phellandrene has been determined by the experiments of Semmler** on the products formed by its oxidation with potassium permanganate and by Wallach's researches on the reactions of the nitrosite. Although much of Wallach's work was anterior to that of Semmler, it will be convenient to consider the latter first.

Unfortunately in his experiments Semmler used a mixture of α - and β -phellandrenes, so that he obtained a somewhat complicated mixture of acids; since, however, the principal constituent of the oil was *l*- α -phellandrene, the oxidation products established fairly conclusively the constitution of this terpene.

The main product was the lactone of a hydroxy dibasic acid,

* Goodway and West, *J.S.C.I.* 1937, **56**, 472 T.

† Simonsen, *Ind. For. Rec.* 1923, **9**, 289.

‡ Smith, Hurst and Reed, *J.C.S.* 1923, **123**, 1657.

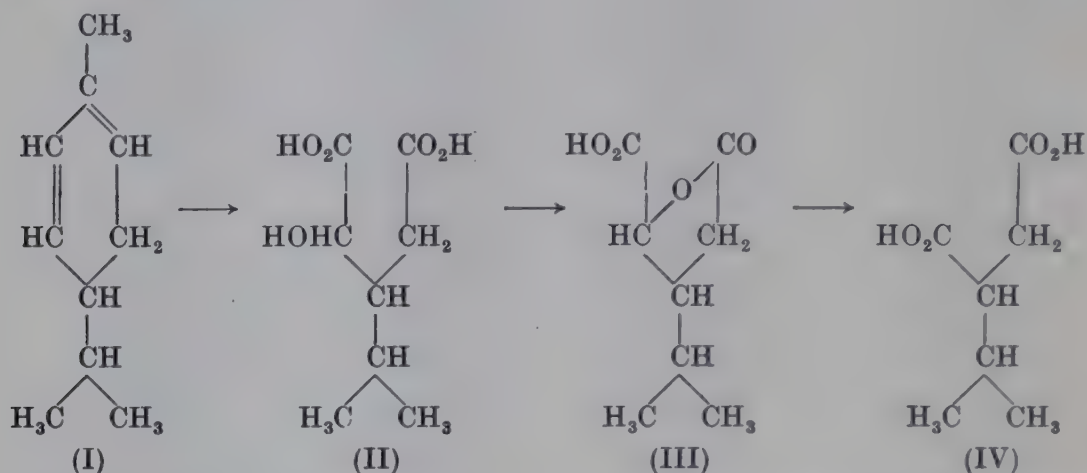
§ Hancox and Jones, *Univ. Queensland Papers*, 1939, **1**, 14.

|| Walbaum and Hüthig, *J. pr. Chem.* 1905 [ii], **71**, 460.

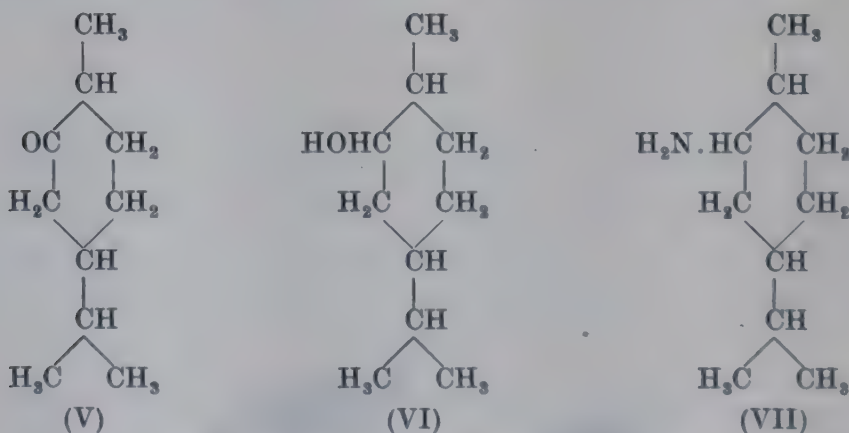
¶ *J. pr. Chem.* 1910 [ii], **82**, 105; *Ber.* 1910, **43**, 816.

** *Ber.* 1903, **36**, 1749.

which was identified as the lactone (III) of *l*- α -hydroxy- β -isopropylglutaric acid (II), since on further oxidation with lead peroxide it gave *l*-isopropylsuccinic acid (IV). The formation of the lactonic acid* was readily explained if *l*- α -phellandrene be represented by (I).



The constitution for α -phellandrene suggested above was fully confirmed by Wallach's investigations, which were mainly carried out with phellandrene from *E. amygdalina*. He had shown in 1895[†] that phellandrene was a derivative of *p*-cymene, since this hydrocarbon was formed when phellandrene dibromide was treated with alkali. In the same communication he described experiments on the reduction of phellandrene nitrosite with sodium and alcohol, when a mixture of *carvomenthone* (V), *carvomenthol* (VI) and *carvomenthylamine* (VII) resulted. These

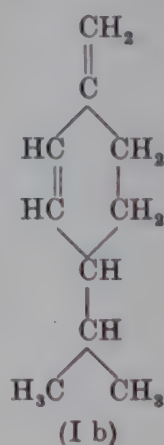
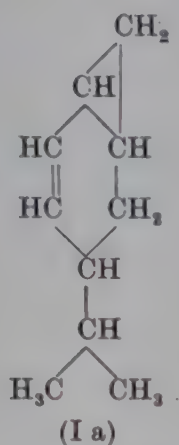
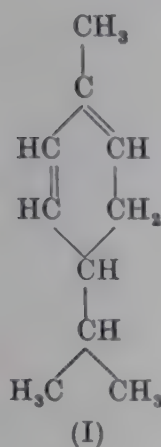


* For a synthesis of the lactone of *dl*- α -hydroxy- β -isopropylglutaric acid, compare Gibson and Simonsen, *J.C.S.* 1929, p. 1079. *l*-isopropylsuccinic acid has been obtained optically pure by Henry and Paget, *J.C.S.* 1928, p. 73.

[†] *Annalen*, 1895, 287, 383.

experiments were carried out with a mixture of α - and β -phellandrenes, since at the time the two terpenes had not been differentiated.

In 1900 Wallach* oxidised phellandrene nitrosite (from *l*-phellandrene) with potassium permanganate and obtained an optically active isopropylsuccinic acid (IV), indicating that phellandrene must have either formula (I), (I a), or (I b).



Four years later Wallach† was able to prove definitely that formula (I) correctly represented α -phellandrene. Taking advantage of the observation of Schreiner,‡ who had shown that phellandrene nitrosite could be separated into isomeric forms, Wallach studied the reduction products which resulted when these nitrosites were treated with zinc and also their behaviour with alkali. During the course of this investigation he was able to establish the constitution of many of the phellandrene derivatives first prepared by Pesci.§

The first important fact which emerged from these researches was that whilst the *l*-phellandrene from *E. amygdalina* and the *d*-phellandrene from bitter fennel and elemi oils were stereoisomerides, the *d*-phellandrene from water fennel oil was a structural isomeride. The two former hydrocarbons were therefore called *l*- α -phellandrene and *d*- α -phellandrene, whilst the latter was designated *d*- β -phellandrene.

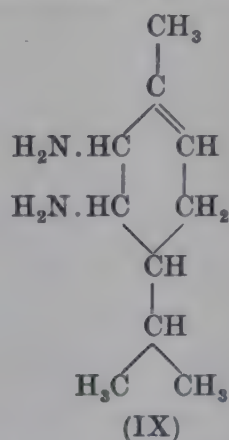
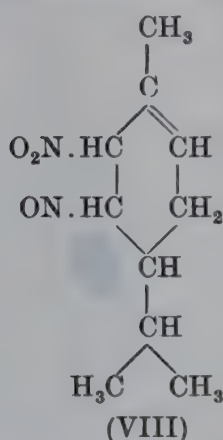
* *Annalen*, 1900, 313, 345.

† *Ibid.* 1902, 324, 271; 1904, 336, 9.

‡ *Pharm. Arch.* 1901, 4, 90.

§ Since Pesci worked with a phellandrene obtained from water fennel oil all the substances prepared by him were derivatives of β -phellandrene.

When the nitrosites from α -phellandrene (either the α - or β -nitrosite) are reduced with zinc in the presence of acetic acid, a *diamine*, b.p. 132–134°/17.5 mm., is obtained. This can be characterised readily by the preparation of the *benzoyl* derivative, m.p. 194–195°, and a *monohydrochloride*, m.p. 209–210°. The diamine was optically active, and the stereoisomeric diamines were respectively obtained, when either *d*- α - or *l*- α -phellandrene was used in the preparation. With the nitrosite of the phellandrene from water fennel oil a completely different diamine was, however, obtained (see p. 207). Adopting formula (I) for α -phellandrene the two nitrosites, probably *cis-trans*-isomerides, may be represented by (VIII)* and the diamine by (IX).

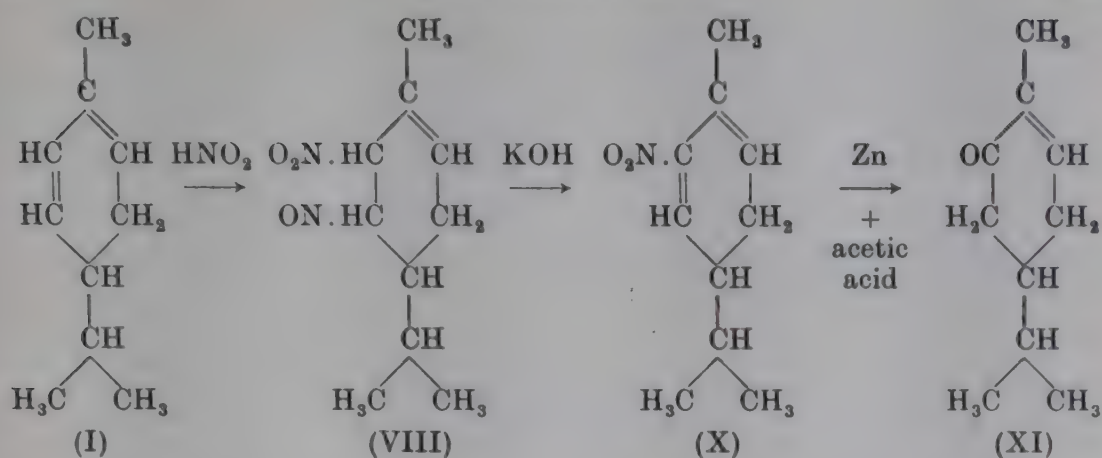


Final proof that formula (I) was correct was furnished by an investigation of the action of alkali on the isomeric α -phellandrene nitrosites. When either of these nitrosites is treated in the cold with an alcoholic solution of potassium hydroxide a *nitro- α -phellandrene* is obtained. This is a pale yellow oil, b.p. 125–129°/9 mm., and is optically active, the direction of rotation depending upon the phellandrene used in its preparation. When this nitro-derivative is reduced with zinc dust in the presence of acetic acid, *d*- or *l*-*curvotanacetone* (XI) is obtained. The formation of this ketone can only be explained if nitro- α -phellandrene has formula (X), the reactions involved in this series of reactions being represented by the scheme given on p. 199.

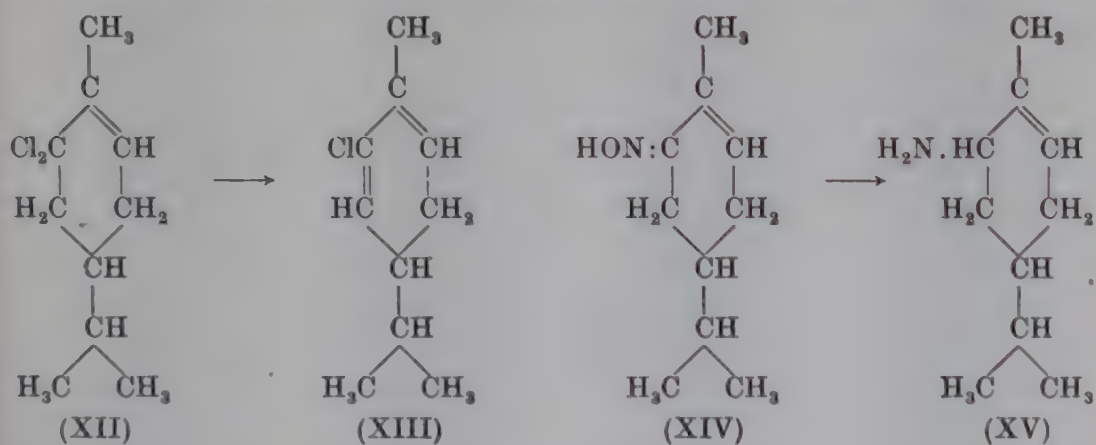
The constitution assigned to α -phellandrene has been confirmed by its synthesis. Harries and Johnson,[†] by treatment of *l*-*curvotanacetone* (XI) with phosphorus pentachloride, prepared

* The nitrosites are bimolecular and formula (VIII) should actually be doubled.

† *Ber.* 1905, 38, 1832.



the *dichloride* (XII), which readily lost hydrogen chloride with formation of the *monochloride* (XIII). The latter on reduction with zinc dust in alcoholic solution gave *d*- α -phellandrene.

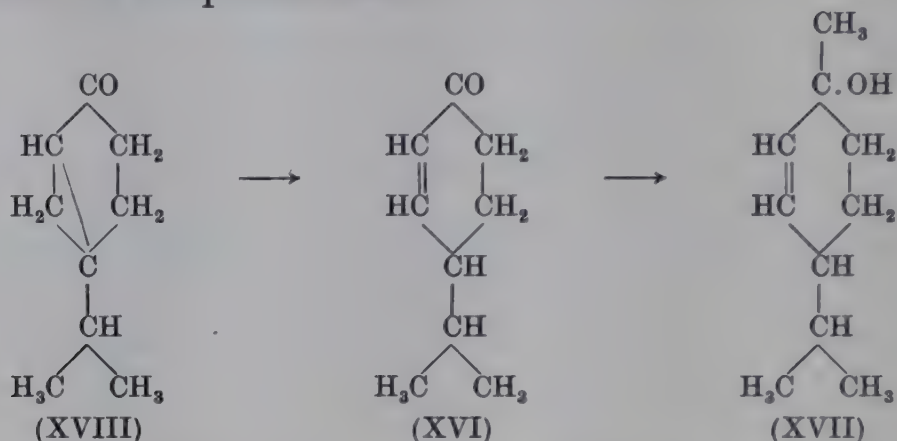


The same authors also synthesised α -phellandrene by the distillation under diminished pressure of the phosphate of the base, 6-amino- Δ^1 -*p*-menthene (XV), which was prepared by the reduction of carvotanacetoxime (XIV).

More recently, the hydrocarbon has been prepared synthetically by Dewar and Read* from *cryptone*, 1-4-isopropyl- Δ^2 -cyclohexen-1-one (XVI) (see p. 334), which with methyl magnesium iodide gave 1-methyl-4-isopropyl- Δ^2 -cyclohexen-1-ol (Δ^2 -*p*-menthen-1-ol) (XVII), and thence, by loss of water, α -phellandrene. The product had b.p. $83\text{--}86^\circ/32\text{ mm.}$, $n_D^{16^\circ}$ 1.4820, $\alpha_D^{16^\circ}$ -53.7° , and gave the crystalline α -nitrosite, m.p. 119° , but was evidently not optically pure. The method is

* *J.C.S.* 1936, p. 1781; compare Wallach, *Annalen*, 1908, 359, 285; Short and Read, *J.C.S.* 1939, p. 1415.

essentially the same as that used by Wallach,* who, however, prepared the ketone (XVI) by isomerisation of *sabinaketone* (XVIII) with dilute acid, and obtained α -phellandrene having only a small dextrorotation. According to Read and Walker† *d*-neopiperitol (p. 288) loses water spontaneously with the formation of *d*- α -phellandrene.



α -Phellandrene can be characterised most conveniently by the preparation of the nitrosite. This substance, the composition of which was first determined correctly by Pesci,* was shown by Schreiner[§] to be a mixture of two nitrosites having different melting-points and opposite rotatory powers. Pure *l*- α -phellandrene- α -nitrosite has m.p. 121° , $[\alpha]_D^{20} + 142.6^\circ$.^{||} *l*- α -Phellandrene- β -nitrosite is very difficult to obtain in a pure state owing to its facile isomerisation into the α -nitrosite. This transformation, which occurs when the β -nitrosite is dissolved in a warm solvent, was discovered by Berry, Macbeth and Swanson[¶] and accounts for the divergent properties recorded for this isomer by earlier workers. As a result of their careful study of the problem, they have prepared a β -nitrosite, m.p. 96° , with a specific rotation (-260°) numerically very much higher than has hitherto been obtained for this substance. They have also obtained** *d*- α -phellandrene- α -nitrosite, m.p. 119° , $[\alpha]_D^{20} - 134^\circ$, and *d*- α -phellandrene- β -nitrosite, m.p. 100° , $[\alpha]_D^{20} + 211^\circ$; the latter is evidently not as pure as the corresponding derivative from *l*- α -phellandrene.

* *Loc. cit.*

† *J.C.S.* 1934, p. 308.

‡ *Jahresbericht*, 1883, p. 1424; 1884, p. 547; 1885, p. 698.

§ *Pharm. Arch.* 1901, 4, 90.

|| Smith, Hurst and Read, *J.C.S.* 1923, 123, 1657; Smith, Carter and Read, *ibid* 1924, 125, 930.

¶ *J.C.S.* 1939, p. 466.

** *Ibid.* p. 1418.

Both the α - and β -nitrosites show marked mutarotation. In the case of *d*- α -phellandrene, the α -nitrosite shows a change of rotatory power in chloroform from -134° to $+86^\circ$ in 33 hours, and the value for the β -nitrosite falls from $+211^\circ$ to 136° in 72 hours in the same solvent.

Wallach* showed the α - and β -nitrosites of *l*- α -phellandrene to be bimolecular; they also give the same α -nitrophellandrene when treated with alkali.

As has already been mentioned, α -phellandrene is somewhat unstable and readily resinifies, the rotatory power rapidly diminishing on exposure to the air. When heated in a sealed tube at about 300° it polymerises to a *diterpene*,[†] b.p. $175-185^\circ/10$ mm., d_D^{20} 0.9125, n_D 1.5061, $\alpha_D -6^\circ$, whilst a mixture of α -phellandrene and isoprene treated similarly gives a *sesquiterpene*, b.p. $129-132^\circ/15$ mm., d^{20} 0.8976, n_D 1.4949, $\alpha_D -15^\circ$. A diterpene[‡] is also obtained, together with α - and γ -terpinenes, when α -phellandrene is shaken with phosphoric acid (*d* 1.75). The properties of this diterpene (b.p. $182-186^\circ/11$ mm., d^{20} 0.9257, n_D^{20} 1.5171, $[\alpha]_D^{20} +14.9$) differ somewhat from those of that prepared by Semmler and Jonas' method.

Reduction of α -phellandrene by hydrogen in the presence of colloidal palladium yields a mixture of *p*-menthane and *p*-menthene, whilst treatment with sodium in alcoholic solution[§] gives Δ^1 -*p*-menthene, b.p. $171-172^\circ$, *d* 0.829, n_D 1.4601.

The autoxidation of the hydrocarbon has been studied by Bodendorf.^{||} The products formed on the oxidation of α -phellandrene with Beckmann's chromic acid mixture have been investigated by Henry and Paget.[¶] They isolated from the reaction mixture two *ketolactones*, $C_{10}H_{16}O_3$ and $C_9H_{14}O_3$, and *thymoquinone*. A study of the properties of the two ketolactones would appear to show that the oxidation proceeds in the following manner. The primary product of the reaction is probably the *alcohol* (XIX), which would pass readily via the *phenol* (XX) into thymoquinone (XXI).

The *ketolactone*, $C_{10}H_{16}O_3$, is probably represented by (XXII).

* *Annalen*, 1895, **287**, 384; 1900, **313**, 345.

† Semmler and Jonas, *Ber.* 1913, **46**, 1567; 1914, **47**, 2078.

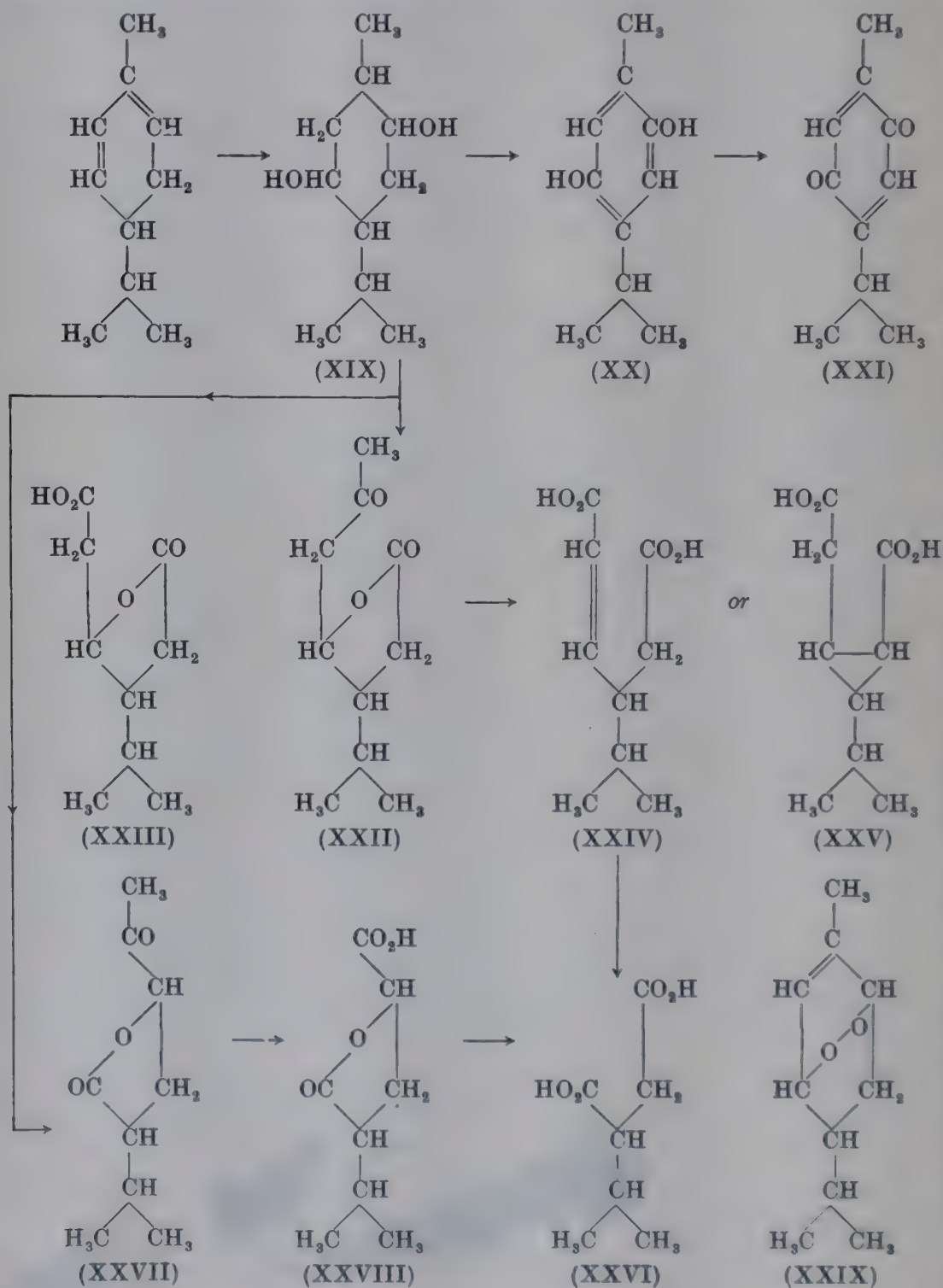
‡ Carter, Smith and Read, *J.S.C.I.* 1925, **44**, 543.

§ Semmler, *Ber.* 1903, **36**, 1035, 1753.

|| *Arch. Pharm.* 1933, **271**, 1.

¶ *J.C.S.* 1928, p. 72.

It behaves abnormally on oxidation with sodium hypobromite solution since, instead of giving the expected *lactonic acid* (XXIII), it is converted into a *dibasic acid*, $C_9H_{14}O_4$, loss of water accompanying the oxidation. This acid may be represented as either the *unsaturated acid* (XXIV) or the *cyclic acid* (XXV).

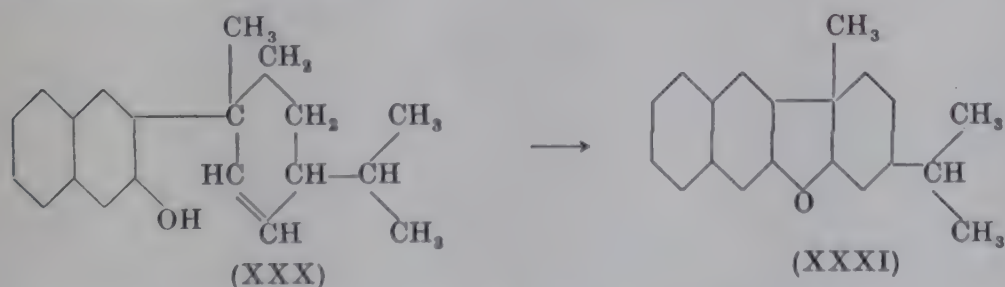


The former formula would appear to be the more probable since the acid readily gives, on further oxidation with potassium permanganate, α -isopropylsuccinic acid (XXVI). A cyclic acid of this structure (XXV) would hardly be expected to behave in this manner. The second *ketolactone*, $C_9H_{14}O_3$, is, in all probability, represented by (XXVII) since, on oxidation with sodium hypobromite, a lactonic acid, $C_8H_{12}O_4$ (XXVIII), is formed, which is readily oxidised to α -isopropylsuccinic acid (XXVI).

It has recently been shown* that α -phellandrene reacts with oxygen when irradiated in the presence of a fluorescent dye to give 1:4-dioxido-2-methyl-5-isopropylcyclohex-2-ene (XXIX), an isomer of ascaridole (p. 446).

With selenium dioxide, α -phellandrene yields cuminaldehyde.[†] Dewar and Read[‡] have shown that *p*-cymene and *p*-menthane are formed when the hydrocarbon is heated with nickel.

The presence of conjugated double bonds in α -phellandrene is supported by its absorption spectrum[§] and by the facile reaction with maleic anhydride to give an adduct, m.p. 126°.^{||} Birch[¶] has applied this reaction to quantitative estimation of α -phellandrene. As would be anticipated, α -phellandrene reacts also with benzoquinone and α -naphthoquinone.^{**} According to Salfeld^{††} α -phellandrene reacts with β -naphthol at 130° to give the *adduct* (XXX), m.p. 139–140°; the presence of a free hydroxyl group in this product is shown by the formation of a *p*-nitrobenzoate, m.p. 164–165°. When the adduct is heated with selenium or with methanolic hydrogen chloride, it undergoes ring closure to give the compound (XXXI).



* Schenck and Ziegler, *Naturwiss.* 1944, **32**, 157.

† Borgwardt and Schwenk, *J. Amer. C.S.* 1934, **56**, 1185.

‡ *J.C.S.* 1936, p. 1781. § Booker, Evans and Gillam, *J.C.S.* 1940, p. 1453.

|| Diels and Alder, *Annalen*, 1928, **460**, 98; Littmann, *J. Amer. C.S.* 1935, **57**, 586; 1936, **58**, 1316; Goodway and West, *J.S.C.I.* 1937, **56**, 472 T.

¶ *J. Proc. Roy. Soc. New South Wales*, 1937, **71**, 54; 1938, **71**, 261.

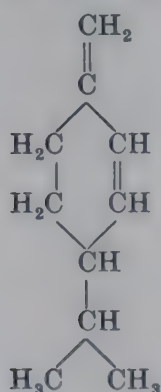
** Diels and Alder, *Ber.* 1929, **62**, 2337.

†† *Ibid.* 1940, **73**, 376.

On treatment with bromine, α -phellandrene yields a liquid dibromide together with a considerable quantity of *p*-cymene.* The investigations of the action of hydrogen chloride on α -phellandrene have led to somewhat contradictory results. According to Wallach† no crystalline hydrochloride can be prepared, but the liquid dihydrochloride yields on treatment with sodium acetate in acetic acid solution a mixture of hydrocarbons containing dipentene. Bacon,‡ working in light petroleum solution, obtained a *monohydrochloride*, 80–83°/10 mm., $d_4^{30^\circ}$ 0.960, $n_D^{20^\circ}$ 1.4770, which on treatment with alkali gave dipentene. These results are somewhat unexpected, since the formation of dipentene requires a curious rearrangement of the ethylenic linkages and the formation of α -terpinene might have been anticipated. Wallach has in fact shown that, with an alcoholic solution of sulphuric acid, α -phellandrene does isomerise to α -terpinene, and a possible explanation of these results is that the α -phellandrene used in these experiments was impure and contained some dipentene.

β -PHELLANDRENE

($\Delta^{1(7):2}$ -p-Menthadiene or
1-Methylene-4-isopropyl- Δ^2 -cyclohexene)



Although, as was mentioned above, the actual phellandrene (α - or β -) occurring in a number of essential oils is not definitely known, there is no doubt that the hydrocarbon studied by Pesci §

* Wallach, *Annalen*, 1895, **287**, 383; Semmler, *Ber.* 1903, **36**, 1753.

† *Annalen*, 1887, **239**, 44; 1889, **252**, 102.

‡ *Philippine J. Sci.* 1909, A, **4**, 105.

§ *Jahresbericht*, 1883, p. 1424; 1884, p. 547; 1885, p. 698.

during the years 1883–5 was β -phellandrene, since it was derived from water fennel oil (from *Phellandrium aquaticum*). It was only many years later that α - and β -phellandrene were differentiated by Wallach.*

d- β -Phellandrene has been shown to occur in water fennel oil, in lemon oil† and the oil from *Bupleurum fruticosum*. The laevo-rotatory form has been found in Japanese peppermint oil and in the oil from *Pinus contorta*; more recently it has been isolated from *E. cneorifolia*‡ and from Canada balsam oil.§

d- β -Phellandrene is a colourless oil with a pleasant odour and a burning taste: b.p. 171–172°; 57°/11 mm., d_{20}^{20} 0.8520, n_D^{20} 1.4788, $[\alpha]_D + 18.54^\circ$. Like α -phellandrene, it is unstable and polymerises if distilled at the ordinary pressure. According to Francesconi and Sernagiotto the pure hydrocarbon has a rotatory power of about $[\alpha]_D + 65.2^\circ$, the lower value generally observed being due to admixture with *dl*- β -phellandrene, and this is supported by the fact that the *l*- β -phellandrene obtained by Smith and West has b.p. 178–179°; 53°/12 mm., d_{15}^{15} 0.8497, n_D^{20} 1.4800, $[\alpha]_D^{20} - 51.9^\circ$. The molecular refraction of the hydrocarbon (obs. 45.36, calc. 45.24) is practically normal, and this fact has been commented upon by Auwers and Eisenlohr,|| since it would be anticipated from the structure of the hydrocarbon, containing as it does a conjugated system of ethylenic linkages, that this value would show a marked exaltation. No reason can at present be assigned for this abnormality.

Like α -phellandrene, β -phellandrene yields a crystalline *nitrosite* which was first prepared by Pesci¶ and subsequently shown by Wallach and Beschke** to be separable into two isomeric forms, *β -phellandrene- α -nitrosite*, m.p. 102°, $[\alpha]_D^{18.5} - 159.3^\circ$ (in chloroform solution) and *β -phellandrene- β -nitrosite*, m.p. 97–98°, which was practically optically inactive. The nitrosite from *l*- β -phellandrene, obtained by Macbeth, Smith and West,†† has m.p. 100°, $[\alpha]_D^{20} + 169^\circ$ in chloroform, falling to $+105^\circ$ after 168 hours.

* *Annalen*, 1902, **324**, 270; 1904, **336**, 10.

† Gildemeister and Müller, *Wallach Festschrift*, 1909, p. 441.

‡ Berry, Macbeth and Swanson, *J.C.S.* 1937, p. 1443.

§ Smith and West, *J.S.C.I.* 1937, **56**, 300 T.

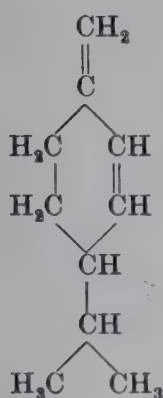
|| *J. pr. Chem.* 1910 [ii], **82**, 106; *Annalen*, 1912, **387**, 253.

¶ *Jahresbericht*, 1883, p. 1424; 1884, p. 547; 1885, p. 698.

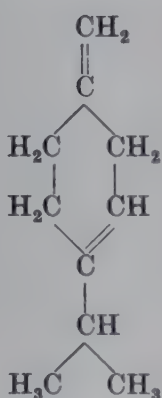
** *Annalen*, 1904, **336**, 43; 1905, **340**, 1.

†† *J.C.S.* 1938, p. 119.

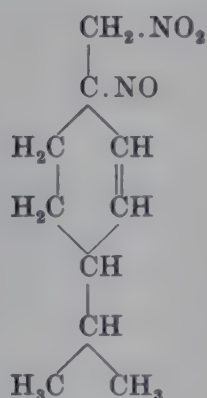
A careful study of the reactions of the nitrosite, which had already been investigated by Pesci, enabled Wallach* to deduce the constitution of the parent hydrocarbon. When β -phellandrene nitrosite (either the α - or β -form) is treated with sodium ethoxide at 30–40° it yields *nitro- β -phellandrene*, a substance which had been prepared previously by Pesci† by the action of ammonia. This nitro-compound, which readily yields salts, cannot be purified by distillation; on reduction with zinc dust in acetic acid solution it yields *dihydrocuminaldehide* and *dihydrocuminylamine*, whilst reduction with sodium and alcohol gives *tetrahydrocuminylamine* and *cuminylamine*.‡ The formation of a partially reduced cuminaldehyde can only be explained by assuming in β -phellandrene the presence of a methylene ($:CH_2$) group with an *isopropyl* group in the para position. There are therefore only two possible formulae, (I) and (I a), of which the second must be incorrect, since it does not allow of optical activity.



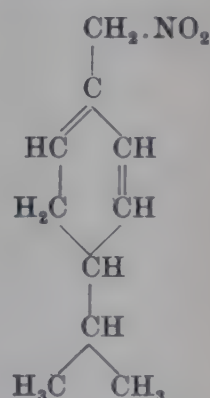
(I)



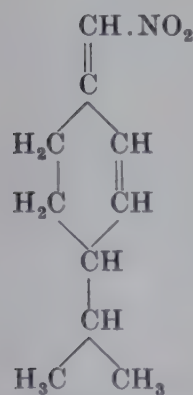
(I a)



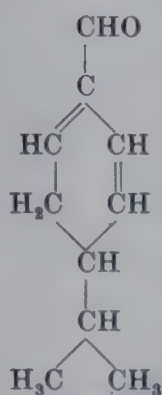
(II)



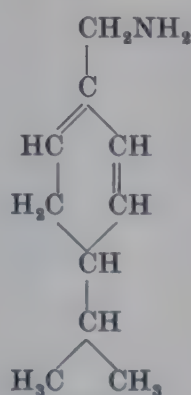
(III)



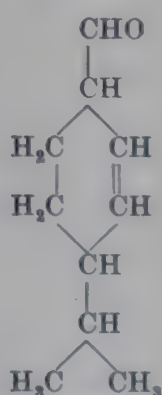
(III a)



(IV)



(V)



(VI)

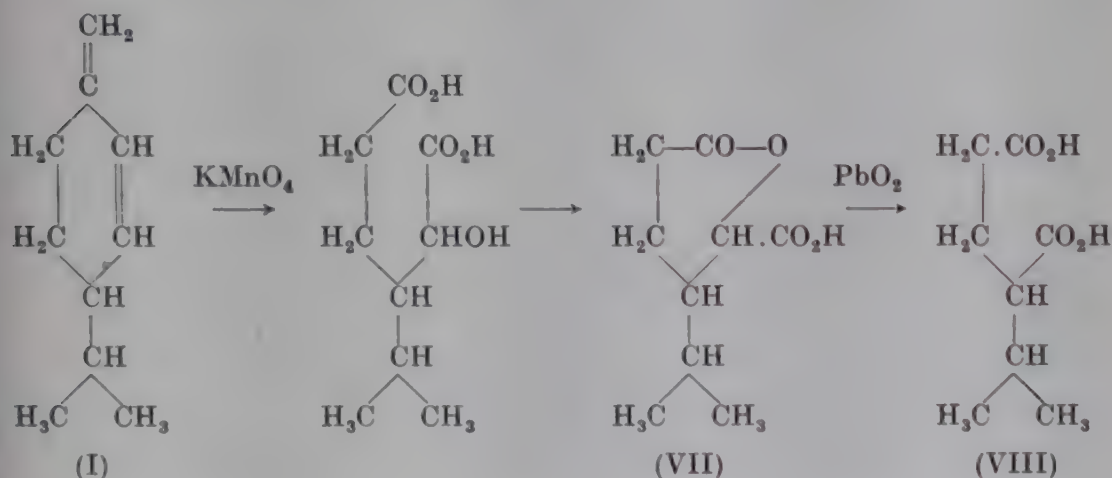
* *Annalen*, 1905, **340**, 1; **343**, 39.

† *Gazzetta*, 1886, **16**, 227.

‡ Macbeth, Smith and West (*loc. cit.*) have obtained cuminal by the direct reduction of *l*- β -phellandrene nitrosite with sodium and alcohol.

It follows from this, that β -phellandrene nitrosite will be represented by (II)* whilst there are two possible formulae, (III) and (III a), for nitro- β -phellandrene. Of these the former is the more probable, since reduction of the nitro-body yields a *dihydro-aldehyde* (IV) and a *dihydro-amine* (V), whereas if (III a) were the correct formula a *tetrahydro-aldehyde* (VI) or *amine* would probably be formed.

This formula for β -phellandrene has been confirmed by a study of its oxidation products. Semmler† showed that, on oxidation with potassium permanganate, the *lactone* of α -hydroxy- β -isopropyladipic acid (VII) was obtained, the constitution of the lactone being proved by its further oxidation with lead peroxide to α -isopropylglutaric acid (VIII).



By the use of a very dilute solution of potassium permanganate at 0° Wallach‡ was able to show that the primary product of the oxidation was a *glycol* (IX). This could not be obtained pure, but its constitution was indicated by the fact that on treatment with dilute sulphuric acid, it gave a *tetrahydrocuminaldehyde* (phellandral), probably having a constitution represented by (X),§ the expected aldehyde (VI) having undergone the well-known $\alpha:\beta\text{-}\beta:\gamma$ change. Macbeth, Smith and West|| have carried out a similar series of transformations on *l*- β -phellandrene.

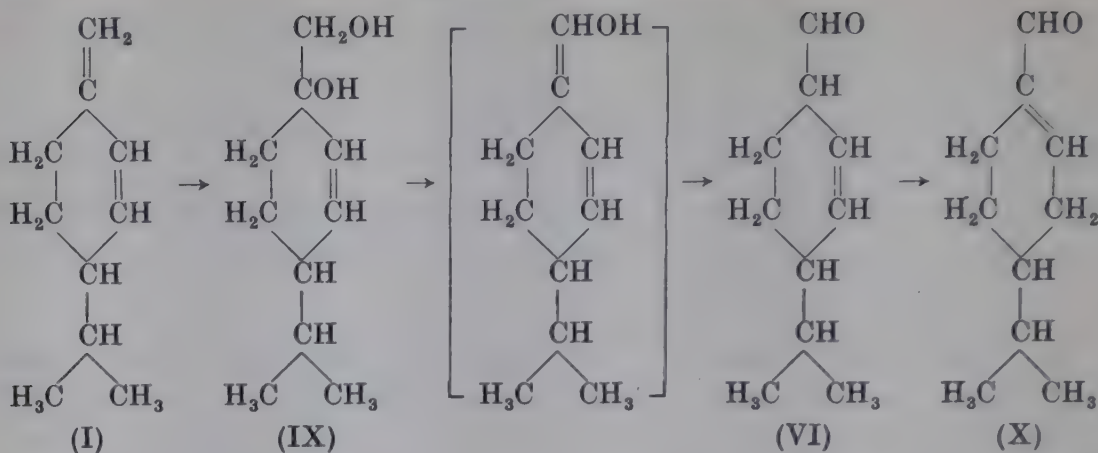
* Actually the nitrosite is bimolecular.

† Ber. 1903, 36, 1749.

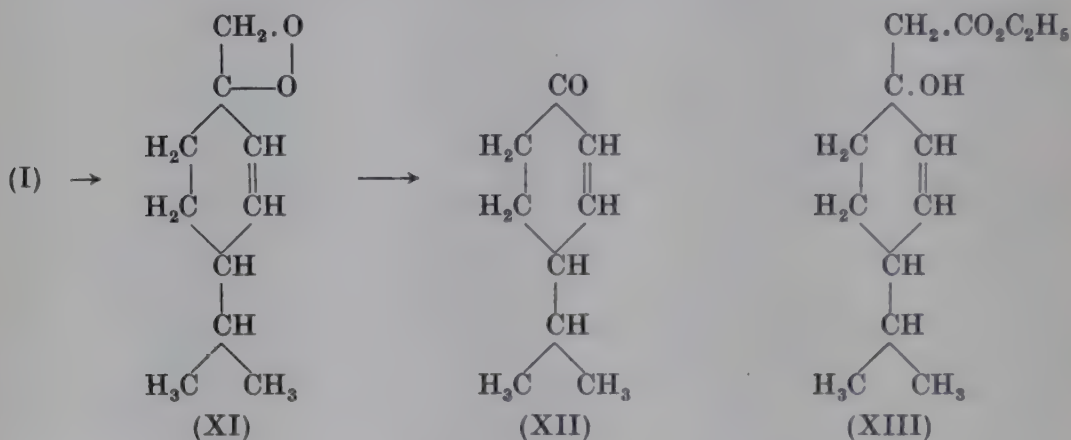
‡ Annalen, 1905, 340, 12; 343, 42.

§ Schimmel's Report, 1909, Oct. p. 51.

|| J.C.S. 1938, p. 119.



Of interest also is the aerobic oxidation* of β -phellandrene in the presence of sunlight, when the ketone 4-isopropyl- Δ^2 -cyclohexen-1-one (XII) is obtained. The peroxide (XI) is probably an intermediate stage in the reaction.



Wallach attempted to synthesise β -phellandrene from the ketone (XII) by condensing it with ethyl bromoacetate in the presence of zinc. The resulting *hydroxy-ester* (XIII) gave on hydrolysis an acid, which, on elimination of carbon dioxide and water, yielded a hydrocarbon showing the reactions of β -phellandrene, but the quantity obtained was insufficient for complete characterisation.

Kondakov and Schindelmeiser[†] claimed to have synthesised β -phellandrene by the following series of reactions. Starting from *p*-menthan-1-ol (XIV) they converted this by loss of water into Δ^1 -*p*-menthene (XV), which, on bromination gave 1:2-

* Wallach, *Annalen*, 1905, **343**, 29; see also Macbeth, Smith and West, *loc. cit.*

[†] *J. pr. Chem.* 1905 [ii], **72**, 193; 1907 [ii], **75**, 141.

the dehydration of the glycol, *terpin*, $C_{10}H_{20}O_2$, yet there was still considerable confusion as to the relationship of these two substances and the conditions governing their interconversion. Much of this obscurity was dispelled by the publication in 1885 by Wallach* of two papers on the action of various dehydrating agents on *terpin* and on the relationship of the products formed in the reaction. He showed that with very weak dehydrating agents the main product was an unsaturated alcohol, *terpineol*,[†] $C_{10}H_{17}OH$. He confirmed Tilden's observation of the formation of a crystalline dichloride and he pointed out that whereas the introduction of one of the halogen atoms was due to the addition of hydrogen chloride to an ethylenic linkage, the other was due to the replacement of a hydroxyl group. Wallach also prepared from the alcohol a crystalline *phenylurethane*.

In the following year Bouchardat and Lafont[‡] made the very important observation that *terpineol* could be obtained crystalline. By heating *dipentene* with acetic acid at 100° for 60 hours they obtained an acetyl derivative from which on hydrolysis an alcohol was prepared, which crystallised when cooled to -50° . This crystalline alcohol, m.p. $30-32^\circ$, was prepared subsequently by Bouchardat and Voiry[§] by the dehydration of *terpin*. With the introduction of the commercial manufacture of a crystalline *terpineol*, m.p. 35° , shown by Wallach^{||} to be identical with that previously investigated by him, the further work on this alcohol was much facilitated.

Constitutional formulae for *terpin* (I) and *terpineol* (II) were first suggested by Brühl,[¶] and these received general acceptance, although certain facts were known which were not quite consonant therewith. It was difficult to account for the oxidation of α -*terpineol* to *terpenylic acid*, the constitution of which had been determined by Schryver,** and an even greater objection was that on dehydration it could only give rise to a hydrocarbon containing no asymmetric carbon atom, whereas actually the

* *Annalen*, 1885, 227, 286; 230, 247.

[†] This name was introduced by Wallach and was subsequently modified by him to α -*terpineol* with the discovery of the isomeric alcohols, β - and γ -*terpineols*, in commercial *terpineol*.

[‡] *Compt. rend.* 1886, 102, 1555.

[§] *Ibid.* 1887, 104, 996; *Bull. Soc. chim.* 1887 [ii], 47, 870; it is not quite certain whether these authors actually obtained α - or β -*terpineol* since both would be present in the mixtures examined by them.

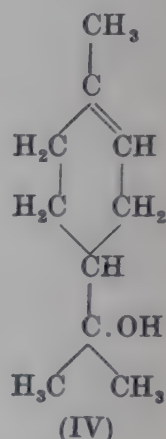
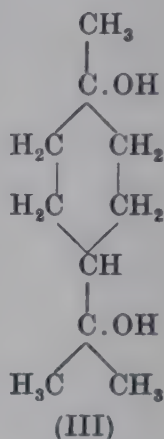
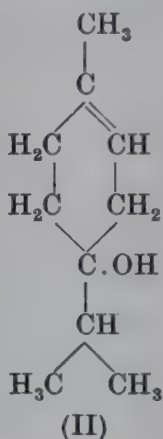
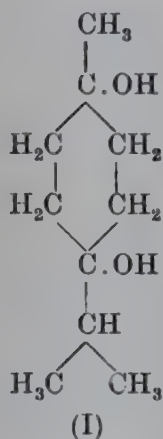
^{||} *Annalen*, 1893, 275, 104.

[¶] *Ber.* 1888, 21, 464.

** *J.C.S.* 1893, 63, 1338.

d- and *l*-forms of the alcohol could be prepared from *d*- and *l*-limonenes. To overcome this latter difficulty Baeyer suggested that the optical activity of the limonenes was due, not to an ϵ symmetric carbon atom, but to the asymmetry of the molecule as a whole.

In 1894 Wagner,* on the basis of his new formula for α -pinene, suggested that terpin and α -terpineol were more correctly represented by (III) and (IV). These formulae were advanced on purely theoretical grounds and were not supported by any fresh direct experimental evidence, but their correctness was very soon recognised, the more especially since the formation of terpenylic acid and other degradation products of α -terpineol was readily accounted for.



The first systematic experiments on the oxidation of *dl*- α -terpineol were made by Wallach,[†] who showed that on oxidation with dilute potassium permanganate, a *glycerol*, $\text{C}_{10}\text{H}_{20}\text{O}_3$, m.p. 121–122°, was obtained in an almost quantitative yield. On dehydration the glycerol gave a mixture of *p*-cymene and the ketone, carvenone, whilst on oxidation with chromic acid a substance, $\text{C}_{10}\text{H}_{16}\text{O}_3$, m.p. 62–63°, was obtained; the latter, by further degradation, gave terpenylic acid. The constitution of the substance, $\text{C}_{10}\text{H}_{16}\text{O}_3$, was not at the time determined, but some years later, after the adoption of Wagner's formula for the alcohol, Wallach[‡] and Tiemann and Semmler[§] simultaneously advanced a correct interpretation of the mechanism of the degradation of α -terpineol.

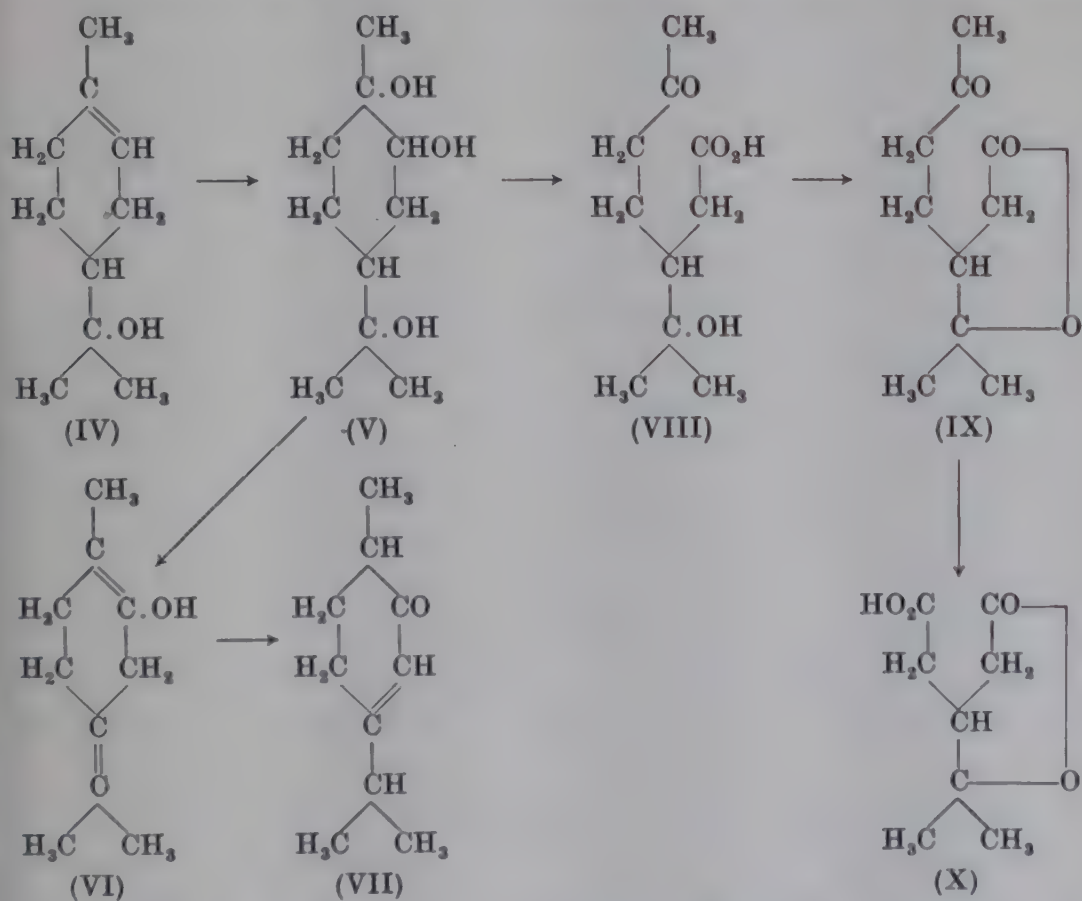
* *Ber.* 1894, **27**, 1652.

‡ *Ber.* 1895, **28**, 1775.

† *Annalen*, 1893, **275**, 151; **277**, 110.

§ *Ibid.* p. 1778.

The primary product of the reaction, the glycerol, was shown to be *p*-menthane-1:2:8-triol (V), the ethylenic linkage having reacted in accordance with the Wagner rule. From this on dehydration *p*-cymene and *carvenone* (VII) were formed, the latter probably by the intermediate stage of (VI). The substance $C_{10}H_{16}O_3$ was shown to be a ketonic lactone, *homoterpenyl methyl ketone* (IX), formed by loss of water from the γ -hydroxy-acid (VIII). This ketone was characterised by the preparation of the *oxime*, m.p. $80-81^\circ$, and the *semicarbazone*, m.p. 200° , whilst the presence of the lactone ring was established by titration with an excess of alkali. The optically active lactonic ketone, m.p. $48-49^\circ$, was first identified by Baeyer and Baumgartel,* although it had been prepared previously by Godlewski† by the degradation of *l*- α -terpineol. The formation of *terpenylic acid* (X) by oxidation of the lactone with potassium permanganate was also readily explained. It may be noted that, contrary to anticipation, homoterpenyl methyl ketone cannot be oxidised with



* Ber. 1898, 31, 3217.

† J. Russ. Phys. Chem. Soc. 1896, 28, 140.

sodium hypobromite to homoterpenylic acid, but undergoes some profound, and at present undetermined, change. The structure of this ketone has been confirmed by synthesis.*

The determination of the constitution of the degradation products left no doubt that the formula suggested by Wagner correctly represented the structure of α -terpineol, and this was fully confirmed by the rational synthesis of the alcohol by W. H. Perkin, jun.,[†] which is described on p. 150.

The constants, more especially the rotatory powers, of the α -terpineols from natural sources, as quoted in the literature, show somewhat wide variations. For a dextrorotatory alcohol derived from oil of sweet oranges Stephan[‡] gives m.p. 38–40°, b.p. 219–221°/760 mm., d^{15}_D 0.938, n^{18}_D 1.4832, $[\alpha]_D + 95.9^\circ$. This alcohol must have been optically pure since Fuller and Kenyon,[§] who prepared the alcohol by the hydrolysis of *d*- α -terpenyl hydrogen phthalate, which had been obtained by the resolution of the *dl*-ester with brucine, found m.p. 36.9°, b.p. 104°/15 mm., d^{14}_D 0.9475, n_D 1.4819, $[\alpha]^{20}_D \pm 100.5^\circ$, whilst Paolini,^{||} who used strychnine for the resolution of the phthalate, gives the rotatory power as $+98.5^\circ$. A much higher value, $[\alpha]_D - 117.5^\circ$, has been recorded by Ertshikowski,[¶] but this is undoubtedly too high. *dl*- α -Terpineol melts at 35°, b.p. 218.8–219.4°/752 mm., d^{20}_{20} 0.935, n^{20}_D 1.4831, and values closely agreeing with these were observed by Kay and Perkin, jun.^{**} for the synthetic alcohol.

α -Terpineol forms a number of crystalline derivatives, so that its identification is easy. Most convenient for this purpose are the *phenylurethane*, *d*- and *l*-forms, m.p. 109.5°, *dl*-, m.p. 113°, and the *nitrolpiperidides*, prepared from the crystalline *nitroschlorides*, *d*- and *l*-, m.p. 151–152°, *dl*-, m.p. 159–160°. The *allophanate*, m.p. 133–134°, has been described by Naves and Grampoloff.^{††}

α -Terpineol can be prepared most conveniently by the dehydration of terpin, for which a great variety of reagents may be employed. In view of the technical importance of the alcohol,

* Owen and Simonsen, *J.C.S.* 1932, p. 1424.

† *J.C.S.* 1904, **85**, 416; Fisher and Perkin, jun., *ibid.* 1908, **93**, 1871.

‡ *J. pr. Chem.* 1900 [ii], **62**, 530.

§ *J.C.S.* 1924, **125**, 2304.

|| *Gazzetta*, 1925, **55**, 804.

¶ *J. Russ. Phys. Chem. Soc.* 1896, **28**, 136; *Bull. Soc. chim.* 1896 [iii], **16**, 1585.

** *J.C.S.* 1906, **89**, 851.

†† *Helv. Chim. Acta*, 1942, **25**, 1500.

which finds an extended application in the perfumery industry, this reaction has been closely studied. The manufacture from terpin was commenced about 1888, as the outcome of the researches of Wallach referred to above, phosphoric acid being used as the dehydrating agent. Since that date numerous modifications in the process have been introduced, for details of which reference must be made to the patent literature. In addition to its manufacture from terpin, α -terpineol can be prepared directly from oil of turpentine (pinene) by the action of sulphuric acid in acetic acid or alcoholic solution, when the optically active modifications of the alcohol are obtained of the same sign as the original hydrocarbon.* Many modifications of this process are described in the technical literature.

When terpineol is prepared by any of these processes a mixture of isomeric alcohols is obtained. This mixture was shown by Stephan and Helle† to be separable by fractional distillation into α - and β -terpineols (compare p. 267); subsequently Wallach and Meister‡ showed terpinen-1-ol also to be present (see p. 279), whilst the investigations of Baeyer (p. 272) indicate the probable occurrence also of γ -terpineol.

In addition to the processes mentioned, *d*-, *l*- and *dl*- α -terpineols have been prepared by a number of other reactions. The alcohol can be obtained by the action of oxides of nitrogen on pinene;§ by the cyclisation of linalool and geraniol with either acetic anhydride, formic acid or a mixture of sulphuric and acetic acids.|| It is formed also by the hydration of dipentene or by the action of dilute alkali on dipentene dihydrochloride, or from terpinene dihydrochloride by treatment with silver acetate followed by hydrolysis of the terpinyl acetate so obtained.¶ Its presence was observed amongst the products formed by the oxidation of α -pinene with hydrogen peroxide,** and Pickard and Kenyon†† obtained it by heating to 170° the additive compound which cineole gives when treated with methyl magnesium iodide.

* Flavitzky, *Ber.* 1887, **20**, 1957; Bertram, *G.P.* 67255.

† *Ber.* 1902, **35**, 2148.

‡ *Annalen*, 1908, **362**, 269.

§ Genvresse, *Compt. rend.* 1901, **132**, 639.

|| Stephan, *J. pr. Chem.* 1898 [ii], **58**, 111; 1899 [ii], **60**, 244; Bertram, *G.P.* 80711

¶ Wallach, *Annalen*, 1906, **350**, 154.

** Henderson and Sutherland, *J.C.S.* 1912, **101**, 2288.

†† *Ibid.* 1907, **91**, 904.

Cineole can also be converted into α -terpineol by digestion with acetic anhydride.*

The catalytic hydrogenation of α -terpineol by the Sabatier-Senderens process with a nickel catalyst gives, according to the experimental conditions used, either dihydroterpineol[†] (see p. 254), *p*-menthane[‡] or *p*-cymene.[§] With a copper catalyst dipentene is said by Neave^{||} to be the main product. Dihydroterpineol can be prepared also by hydrogenation in the presence of colloidal palladium.[¶]

The oxidation of α -terpineol with ozone has been found by Harries^{**} to give the normal ozonide, $C_{10}H_{17}OH(O_3)$, but with nitric acid there is very complete degradation with formation of *terpenylic* and *terebic acids*, the former acid, together with homoterpenyl methyl ketone, being obtained with chromic acid.^{††} With Caro's reagent, Baeyer and Villiger^{**} obtained the same glycerol as is formed by the action of potassium permanganate. The autoxidation of α -terpineol has been studied by Dupont.^{§§}

With bromine α -terpineol gives in acetic acid solution a liquid *dibromide* (XI),^{|||} which was found by Baeyer to react with hydrogen bromide to give a tribromide, 1:2:8-*tribromo-p-menthane* (XII).

This bromide was also an oil and it is interesting to note that on further bromination it gives *dipentene tetrabromide* (XIII), a reaction which implies either elimination of hydrogen bromide followed by addition of bromine to the ethylenic linkage so formed, or else direct bromination of the methyl group, which would appear improbable.

The dibromide is not stable, and on warming is converted into *p*-cymene,^{¶¶} an example of the method introduced by Baeyer and Villiger for the dehydrogenation of cyclic bodies by exhaustive bromination.

* Knoevenagel, *Annalen*, 1914, **402**, 141.

† Béhal, *Compt. rend.* 1910, **150**, 1763.

‡ Haller and Martine, *Compt. rend.* 1905, **140**, 1298.

§ Sabatier and Gaudion, *Compt. rend.* 1918, **168**, 671.

|| J.C.S. 1912, **101**, 514.

¶ Wallach, *Annalen*, 1911, **381**, 55.

** Ber. 1912, **45**, 942; compare Briner, Mottier and Paillard, *Helv. Chim. Acta*, 1930, **13**, 1030.

†† Tiemann and Schmidt, *Ber.* 1895, **28**, 1783.

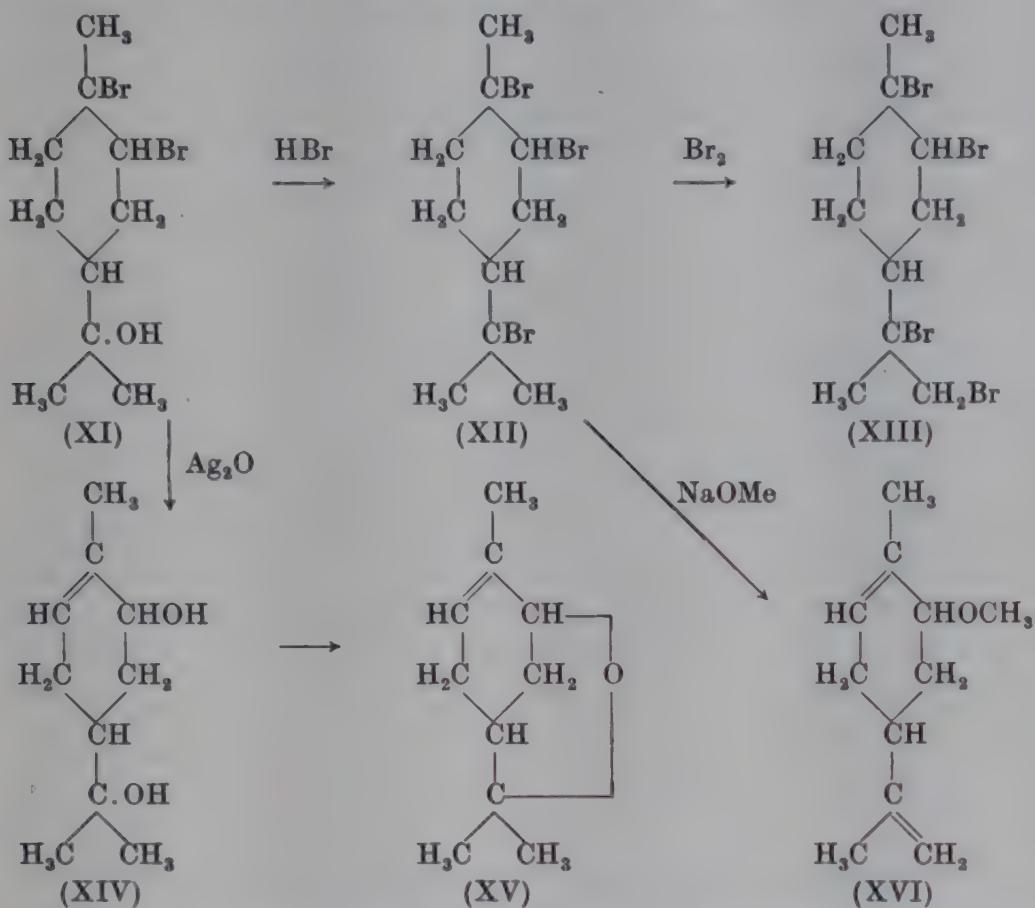
** Ibid. 1899, **32**, 3633.

§§ *Ind. chim. belge*, 1940 [2], **11**, 3.

||| Wallach, *Annalen*, 1893, **277**, 113.

¶¶ Wallach, *ibid.* 1918, **414**, 206.

When the dibromide was treated with silver oxide, it was found by Wallach* to give a mixture of *pinol hydrate* (XIV) and *pinol* (XV), whilst, from the tribromide by the action of sodium methoxide, *carveol methyl ether* (XVI) was prepared.†



With sodium hypochlorite α -terpineol gives two isomeric *chlorohydrins*, m.p. 114–115° and 60–80°,‡ which are probably *cis-trans*-isomerides. With the halogen acids, the alcohol yields the corresponding dipentene dihalogenides.

The elimination of water from α -terpineol takes place with great ease and in all cases a mixture of hydrocarbons is produced. With potassium bisulphate or active carbon the main product is dipentene, whilst formic acid and aqueous oxalic acid are stated to give chiefly terpinolene; in every case, however, terpinene is also formed in not inconsiderable quantity.§ The

* *Annalen*, 1893, 277, 113; compare Slawinski and Hofszajn, *Schimmel's Report*, 1931, p. 170.

† *Annalen*, 1894, 281, 141.

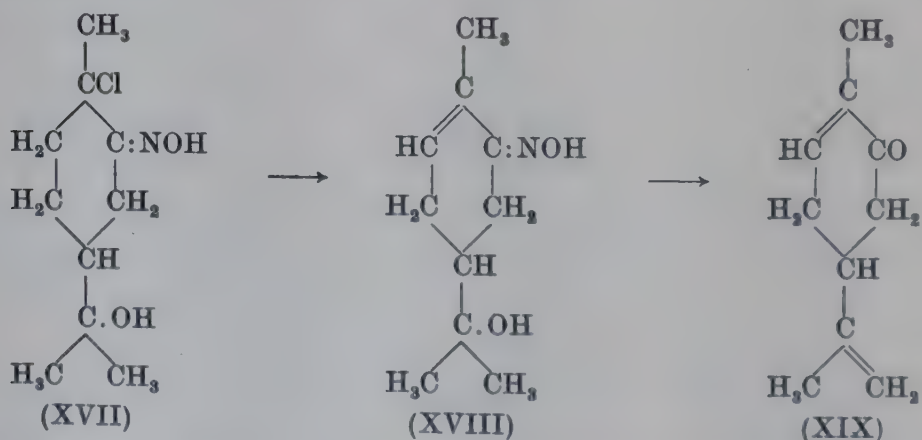
‡ Slawinski, *Chemik Polski*, 1917, 15, 97.

§ Wallach, 1885, 230, 225; 1893, 275, 104; 1896, 291, 361; Baeyer, *Ber.* 1894, 27, 447; Kimura, *Bull. Chem. Soc. Japan*, 1935, 10, 330; Alder and Rickert, *Ber.* 1937, 70, 1364; Ipatiev and Pines, *J. Amer. C.S.* 1944, 66, 1120.

dehydration of α -terpineol to dipentene with comparatively little isomerisation can apparently be effected conveniently with methyl magnesium iodide, but even this reagent causes almost complete racemisation.* Fuller and Kenyon† have, however, found that when either *d*- or *l*- α -terpenyl hydrogen phthalates are hydrolysed with alkali, considerable conversion into *d*- and *l*-limonenes occurs with practically no racemisation.

As was first observed by Tilden,‡ when α -terpineol is allowed to remain in contact with dilute mineral acids it is hydrated with formation of terpin; Aschan§ has shown that the change is almost quantitative with sulphuric acid (40 per cent.) at 0°.

α -Terpineol nitrosochloride (XVII), which is bimolecular, was prepared by Wallach.|| The *d*- and *l*-forms melt at 107–108° and the *dl*- at 120–122°; more convenient for identification are, however, the nitropiperidides (compare p. 260). When the nitrosochlorides are treated with sodium methoxide, 8-hydroxycarvotanacetoxime (XVIII), m.p. 133–134°, is obtained, which is converted by the action of dehydrating agents into *carvone* (XIX) or by the action of concentrated mineral acids into aminothymol.¶



The *semicarbazone* of 8-hydroxycarvotanacetone is obtained when the nitrosochloride is heated with semicarbazide hydrochloride, α -terpineol being also formed. The reaction proceeds obviously with the prior formation of the ketone, which then reacts with the excess of semicarbazide. Of interest also is the

* Fisher and Perkin, jun., *J.C.S.* 1908, 93, 1875.

† *Ibid.* 1924, 125, 2304.

‡ *Ibid.* 1879, 35, 289.

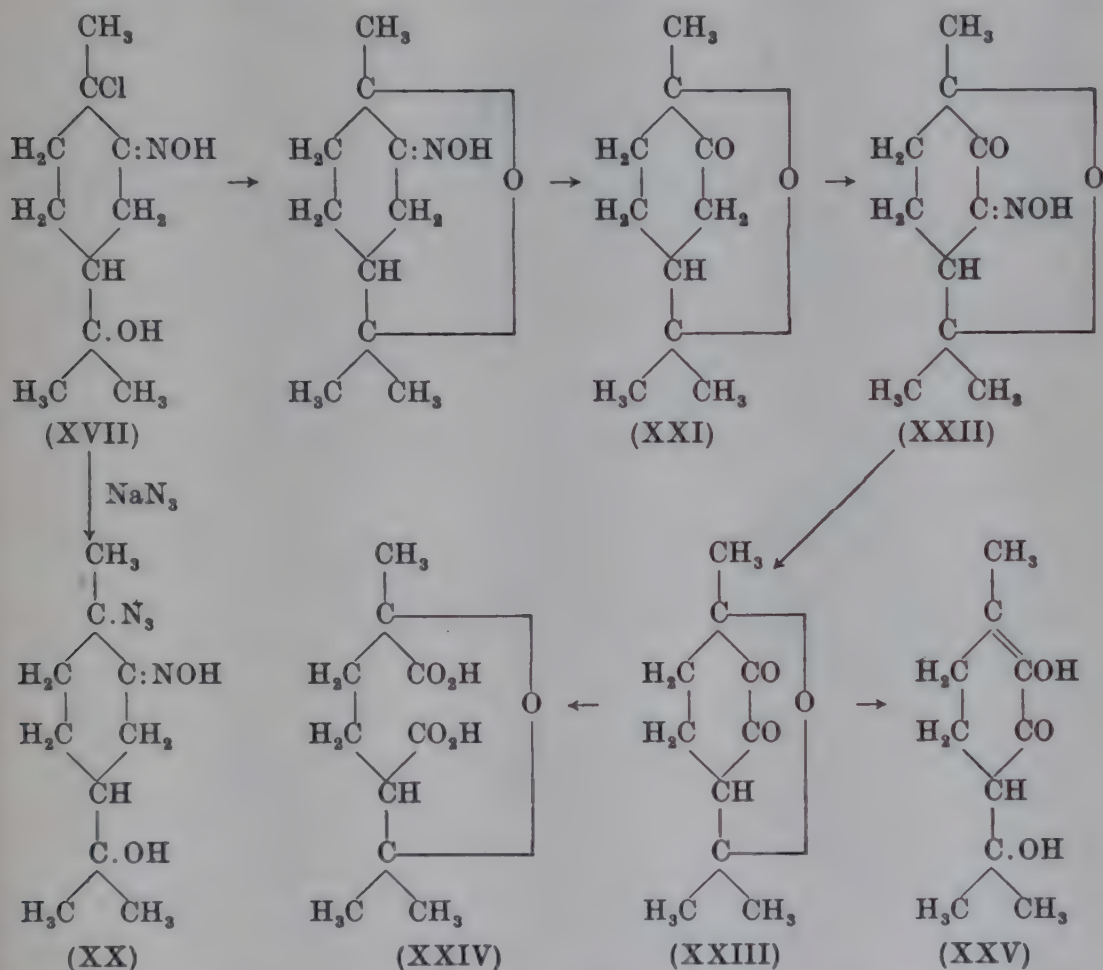
§ *Bidrag til Kännedom af Finland*, 1918, 77, 1.

|| *Annalen*, 1893, 277, 120.

¶ Wallach, *ibid.* 1906, 345, 128.

interaction of the nitrosochloride with sodium azide, yielding α -terpineol nitrosoazide (XX), m.p. 111° , from which by the action of alkali the hydroxy-ketone can be prepared.*

Cusmano[†] has found that by the action of alcohol on the nitrosochloride, *keto-cineole* (XXI) (*d*-, m.p. 50° ; *dl*-, m.p. 42°) is produced. The reactions of this substance have been studied in some detail and of particular interest is its conversion through its isonitroso-derivative (XXII), m.p. 132° , into the



yellow *diketo-cineole* (XXIII). This gives *cineolic acid* (XXIV) on oxidation and on reduction *hydroxydiosphenol* (XXV). The conversion of keto-cineole into diosphenol is referred to on p. 418. Reduction of keto-cineole gives two isomeric *hydroxycineoles*, m.p. 80° and 108° .[‡]

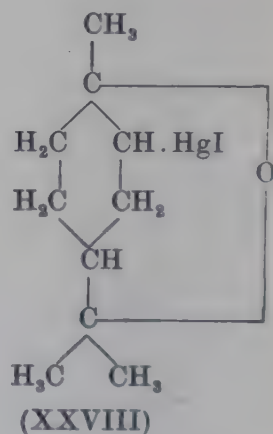
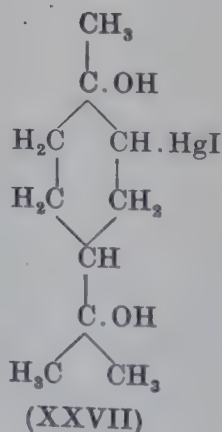
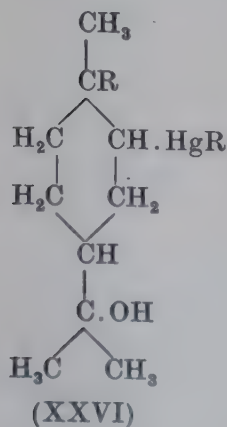
* Forster and Newman, *J.C.S.* 1911, **99**, 250.

† *Gazzetta*, 1919, **49**, I, 26; 1923, **53**, I, 195; 1925, **55**, 140; 1942, **72**, 68.

‡ Ishidate, *J. pharm. Soc. Japan*, 1928, **48**, 9; Gandini, *Gazzetta*, 1937, **67**, 113.

In addition to those separated from essential oils, a large number of esters of α -terpineol has been prepared, since they are of technical importance. These do not require special mention, but attention must be directed to the fact that the usual methods of esterification do not give good yields, owing to the tendency for dehydration to occur with formation of dipentene and other hydrocarbons. The *formate* and *acetate* are conveniently prepared by the action of formic acid and acetic anhydride respectively on either pinene or geraniol.* Direct preparation of the esters from the alcohol can be effected in excellent yield from the potassium salt. In this manner Fuller and Kenyon† prepared dl- α -terpenyl hydrogen phthalate, m.p. 117–118°, which could be readily resolved by strychnine into its optical enantiomorphs. These authors also prepared and studied the rotatory powers of a number of optically pure esters. The *methyl ether* of α -terpineol has been prepared by Treibs‡ by the action of methyl alcohol and sulphuric acid on α - and β -pinenes.

Mercury derivatives of α -terpineol have been obtained by Sand and Singer§ by the action of mercury salts on the alcohol in alkaline solution. These compounds have the general formula (XXVI) ($R = \text{Cl, Br or I}$) and, when treated with an aqueous solution of potassium iodide, give a mixture of trans-*terpin mercuri-iodide* (XXVII) and the *mercuri-iodide* derivative of cineole (XXVIII).



* Lafont, *Bull. Soc. chim.* 1888 [ii], **49**, 325; Lafont and Bouchardat, *Ann. chim.* 1889 [vi], **16**, 244; Stephan, *J. pr. Chem.* 1899 [ii], **60**, 244; compare Paillard and Tempia, *Helv. Chim. Acta*, 1931, **14**, 1314.

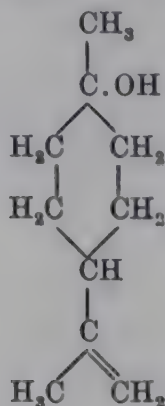
† *J.C.S.* 1924, **125**, 2304.

‡ *Ber.* 1937, **70**, 593.

§ *Ibid.* 1902, **35**, 3170; *Annalen*, 1903, **329**, 141.

β -TERPINEOL

($\Delta^{8(9)}$ -p-Menthen-1-ol or 1-Methyl-4-isopropenylcyclohexan-1-ol)



β -Terpineol, $C_{10}H_{18}O$, has not been found to occur in nature. It was first separated in a pure state from the lower boiling fraction of commercial "terpineol" by Stephan and Helle,* although it is not improbable that the alcohol, m.p. $30-32^\circ$, which Bouchardat and Voiry† prepared by the action of dilute sulphuric acid on terpin hydrate, was identical with β -terpineol.

By prolonged fractional distillation of "terpineol" Stephan and Helle succeeded in separating two fractions: (i) b.p. $212-215^\circ$, d^{15}_4 0.930, and (ii) b.p. $218-220^\circ$, d^{15}_4 0.940. The higher boiling fraction consisted essentially of α -terpineol, m.p. 35° , whilst the lower boiling fraction on cooling deposited β -terpineol, m.p. $32-33^\circ$.

The constitution of the alcohol was shown to be represented by (I) by an investigation of the products formed on oxidation with dilute potassium permanganate.‡ The primary product is the crystalline glycerol, p-menthane-1:8:9-triol (II), m.p. $118-118.5^\circ$, which, on further oxidation with chromic acid, gives the hydroxy-ketone (III) (b.p. $140-145^\circ/19$ mm., semicarbazone, m.p. $195-196^\circ$) together with the unsaturated ketone (IV) (b.p. $68.5-70^\circ/4$ mm., semicarbazone, m.p. 160°).

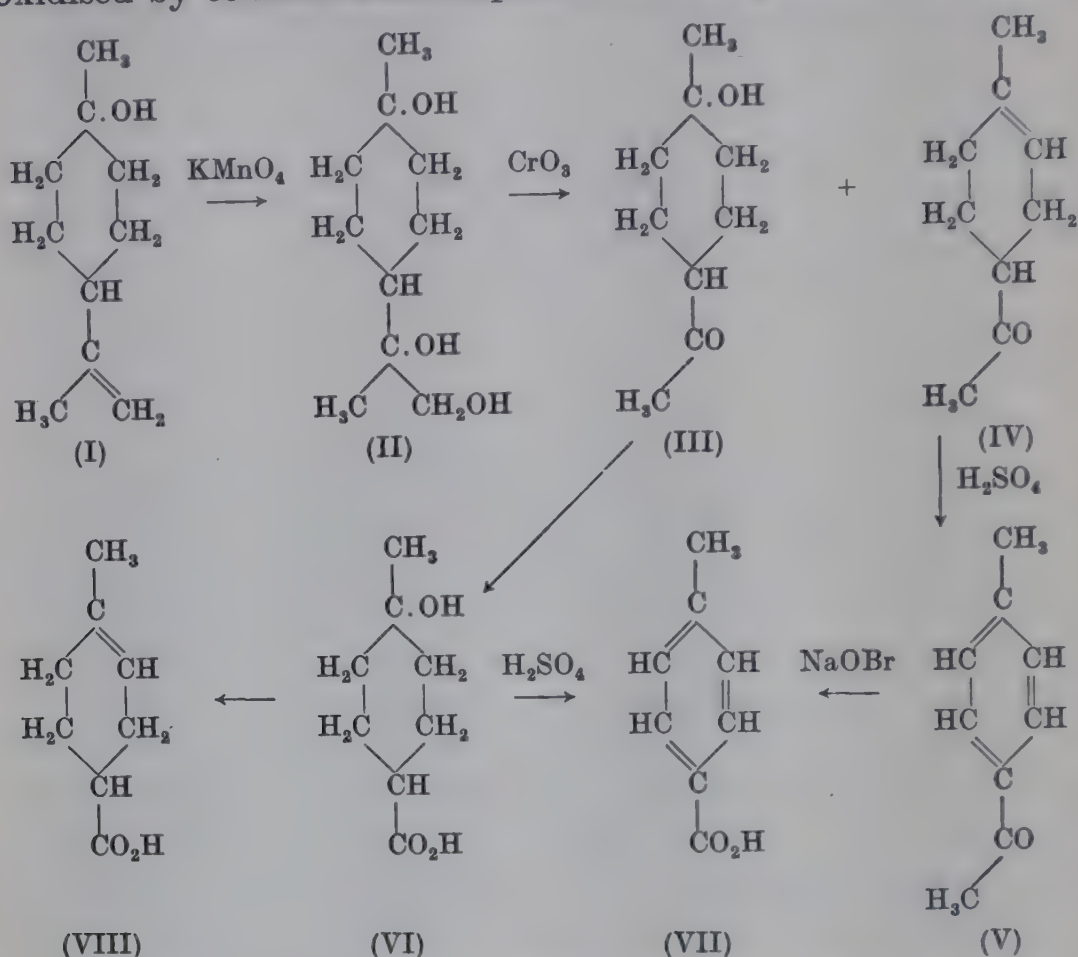
By the action of concentrated sulphuric acid the unsaturated ketone can be converted into p-tolyl methyl ketone (V), whilst oxidation of the hydroxy-ketone (III) with sodium hypobromite yields 1-methylcyclohexan-1-ol-4-carboxylic acid (VI). This hy-

* Ber. 1902, 35, 2148.

† Compt. rend. 1887, 104, 996; Ann. chim. 1887 [vi], 11, 562.

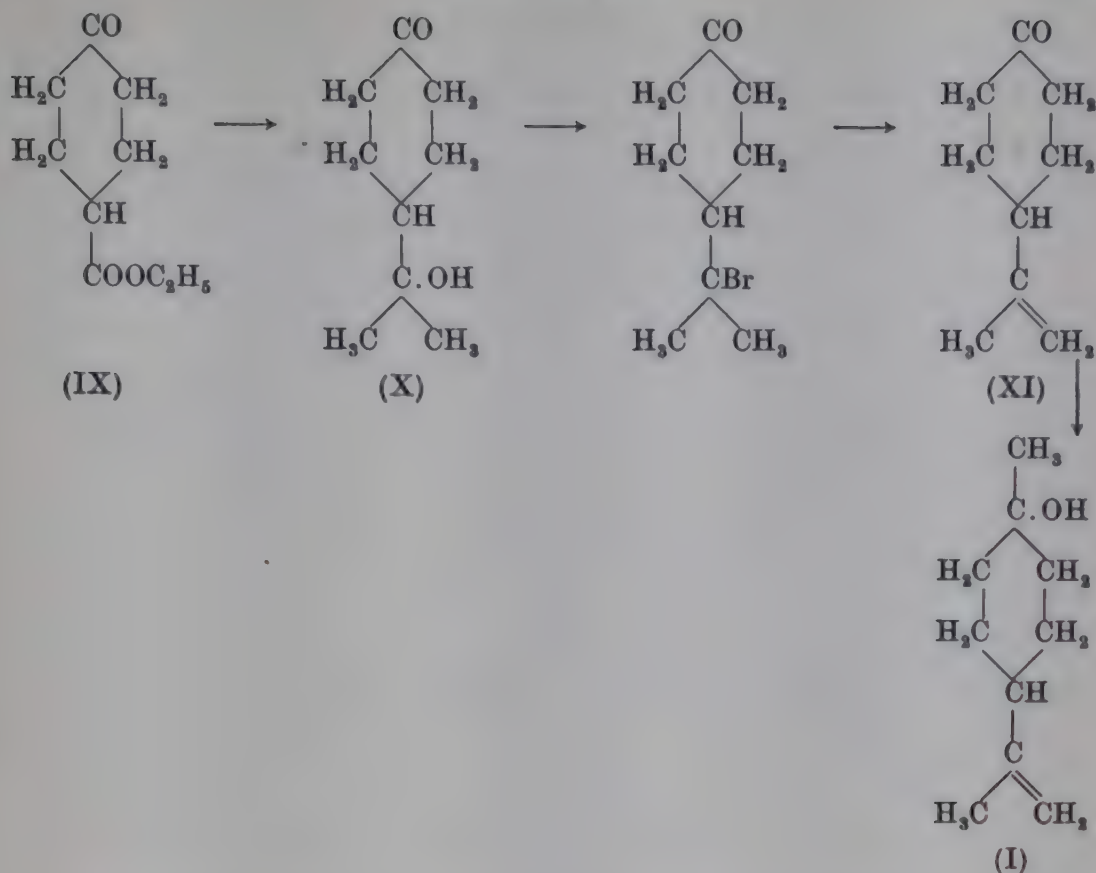
‡ Stephan and Helle, loc. cit.; Wallach and Rahn, Annalen, 1902, 324, 87; Wallach, ibid. 1910, 374, 206; 1911, 381, 90.

droxy-acid, which gives a crystalline *lactone*, m.p. 69–70°, is oxidised by concentrated sulphuric acid to *p*-toluic acid (VII).



Whilst these degradation products leave little doubt as to the constitution of the parent alcohol, its synthesis, which was accomplished by W. H. Perkin, jun.,* in the course of that of α -terpineol, is of great interest. It may be mentioned that incidentally Perkin also synthesised the two acids represented by formulae (VI) and (VIII). By the action of methyl magnesium iodide on *ethyl cyclohexan-4-one-carboxylate* (IX) the *hydroxy-ketone* (X), b.p. 177–180°/100 mm., was obtained and this, by treatment with hydrogen bromide followed by an alcoholic solution of potassium hydroxide, gave the unsaturated ketone, 4-isopropenylcyclohexan-1-one (XI). When this ketone was treated with methyl magnesium iodide, β -terpineol (I) was obtained, which was identified by conversion into the characteristic *phenylurethane*, m.p. 83–85°.

* J.C.S. 1904, 85, 670.



β -Terpineol melts at $32-33^\circ$, b.p. $209-210^\circ/752\text{ mm.}$, $d_{20}^{20} 0.919$, $n_D^{20} 1.4747$; it has a strong odour of hyacinths. The alcohol should exist in *cis-trans*-modifications, but only one form has been described. It can be characterised by the preparation of the *phenylurethane*, m.p. 85° , referred to above.

A further interesting synthesis of the alcohol has been described by Wallach,* who has shown that the unsaturated ketone (IV) when treated with methyl magnesium iodide gives β -terpineol.

On catalytic hydrogenation,[†] the alcohol is converted into *p-menthan-1-ol* (XII), a substance first prepared by Baeyer[‡] by the hydration of *carvomenthene* (Δ^1 -*p-menthene*) (XIII).

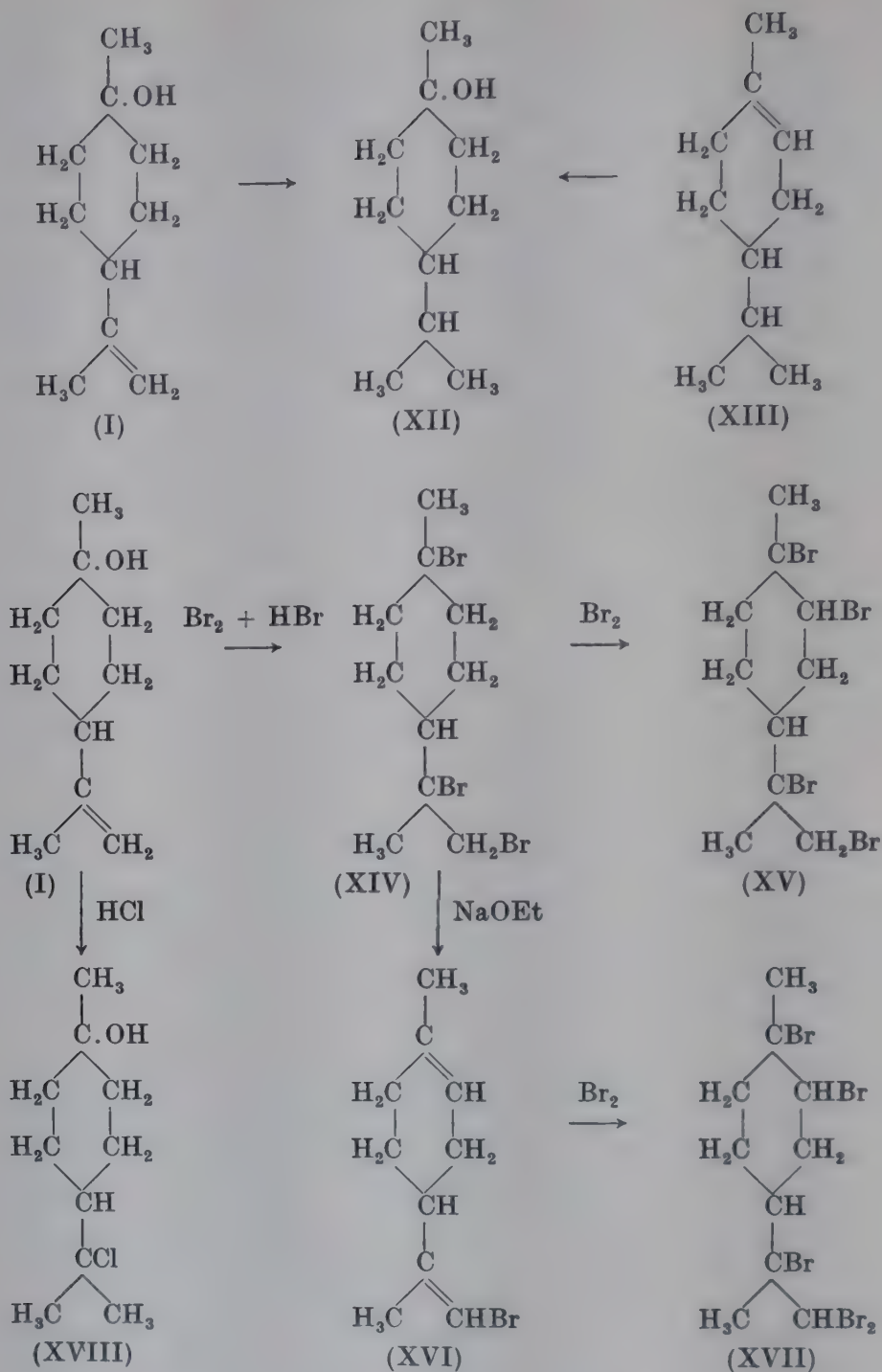
When β -terpineol is treated in acetic acid solution with one mole of bromine and the product then allowed to react with hydrogen bromide, Wallach[§] showed that a crystalline tri-bromide, 1:8:9-*tribromo-p-menthane* (XIV), m.p. 67° , is formed, which, by the further action of bromine, gives *dipentene tetrabromide*.

* *Annalen*, 1917, **414**, 206.

‡ *Ber.* 1893, **26**, 2270.

† Wallach, *ibid.* 1911, **381**, 58.

§ *Annalen*, 1902, **324**, 82.



If the tribromide is treated with sodium ethoxide, it yields a liquid *monobromide* (XVI), b.p. $105\text{--}110^\circ/10\text{ mm.}$, from which on bromination the *pentabromide* (XVII), m.p. 137° , can be prepared.

By the action of an excess of halogen acids on the alcohol the dipentene dihalogenides are obtained, but, if only one mole

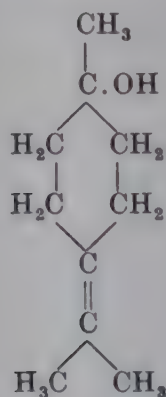
of hydrogen chloride in alcoholic solution is used, a *chlorohydrin* (XVIII), m.p. 74–75°, can be isolated, which with alkalis gives *cis*-terpin.*

By hydration with dilute sulphuric acid terpin hydrate is obtained, the reaction proceeding according to Wallach† much more rapidly than is the case with α -terpineol.

β -Terpineol nitrosochloride‡ melts at 102–103° and does not react very readily with bases, the most satisfactory derivative being the *nitrolanilide*, m.p. 110°. The *nitrosate*, m.p. 125°, and the *nitrosite*, m.p. 78°, have also been prepared. By the action of alkali on the nitrosochloride a hydroxy-oxime is obtained, which cannot, however, be readily purified. When the oxime is hydrolysed with oxalic acid it yields, according to Wallach and Schmitz,§ an aldehyde, whilst with mineral acids a ketone is formed. The constitution of these two substances has not been determined.

γ -TERPINEOL

(Δ^4)-p-Menthen-1-ol or
1-Methyl-4-isopropylidenecyclohexan-1-ol)



The occurrence in nature of the alcohol, γ -terpineol, has not been definitely proved, but according to Simonsen^{||} it probably occurs in small quantity in the essential oil from the leaves of *Cupressus torulosa* Don.

* Wallach, *Annalen*, 1906, **350**, 158.

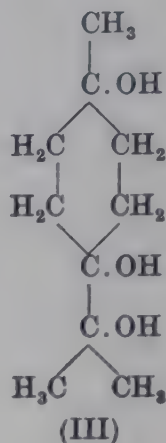
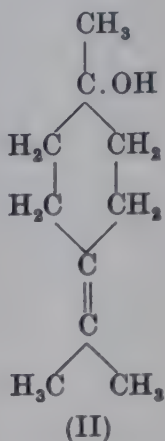
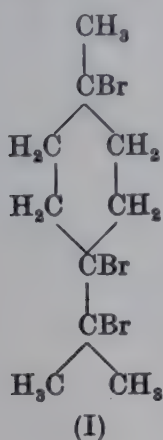
† *Ibid.* 1908, **360**, 101.

‡ Stephan and Helle, *loc. cit.* p. 2150; Wallach and Schmitz, *Annalen*, 1906, **345**, 128.

§ *Annalen*, 1906, **345**, 128.

|| *Ind. For. Rec.* 1923, **10**, 1.

γ -Terpineol was prepared in a pure state by Baeyer and our knowledge of its chemistry is due almost entirely to his investigations. He showed in 1894* that when 1:4:8-tribromo-p-menthane (I), the preparation of which is described on p. 170, was reduced with zinc dust in acetic acid solution, the acetate of an unsaturated alcohol was formed which on hydrolysis gave a new crystalline alcohol, γ -terpineol (II).



Shortly afterwards† he showed that it was present also in the mixture of alcohols which results from the dehydration of *cis*-terpin with either phosphoric or oxalic acids. The evidence on which the constitutional formula for γ -terpineol is based has already been discussed (p. 170) and need not be recapitulated here.

γ -Terpineol crystallises from ether in thick prisms, m.p. 68–70°; the boiling-point of the alcohol does not appear to have been determined, although Baeyer remarks that it can be distilled without decomposition. It resembles α -terpineol in odour.

Apart from the early investigations of Baeyer and his collaborators, the properties of the alcohol have been little studied; probably the most suitable derivative for its characterisation is the *dibromide*, m.p. 114–115°‡

The action of reducing agents on the alcohol has not been investigated, but, on oxidation with potassium permanganate, it gives in excellent yield the glycerol, p-menthane-1:4:8-triol (III), m.p. 110–112°, which can be converted into the tribromide (I) by the action of hydrogen bromide.

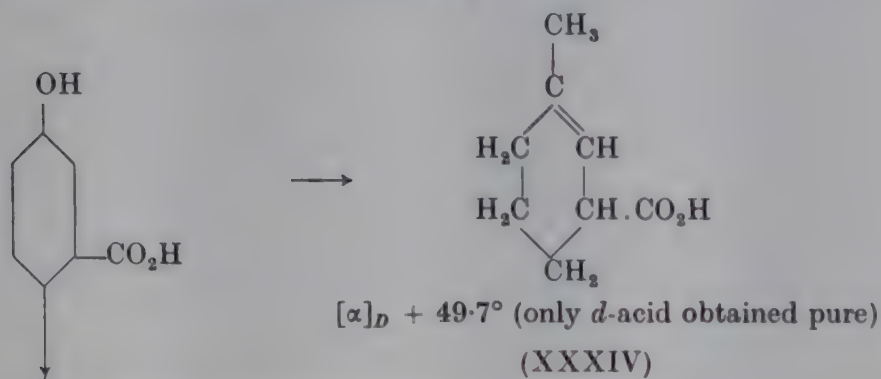
* *Ber.* 1894, 27, 443.

† *Ibid.* 1894, 27, 815.

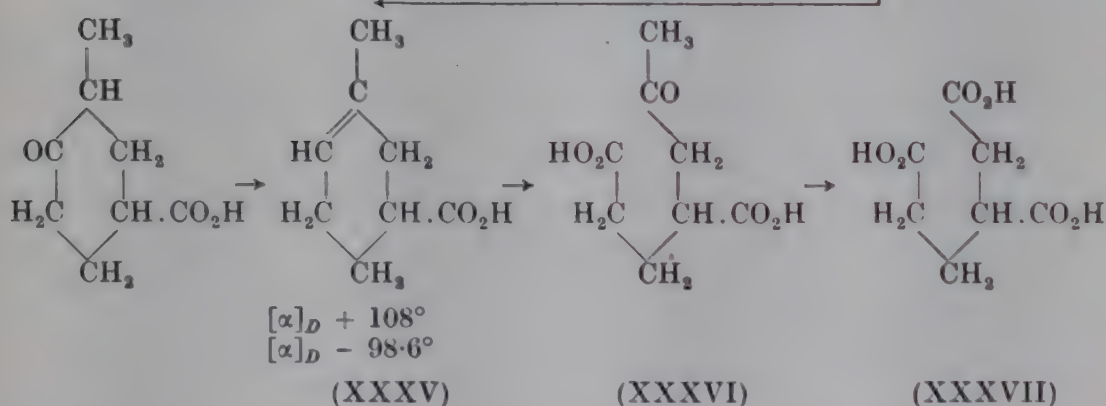
‡ Baeyer and Blau, *ibid.* 1895, 28, 2296.

formula (XXXIV). When this acid was resolved into its optically active enantiomorphs it was found, contrary to the view of Perkin and Tattersall, to be a mixture of two acids, one

I. *Perkin and Tattersall* (compare p. 219).



II. *Fisher and Perkin* (compare p. 220).

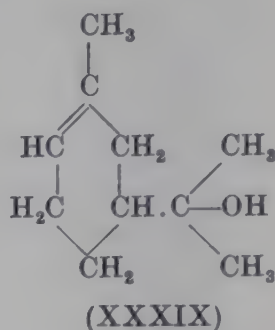
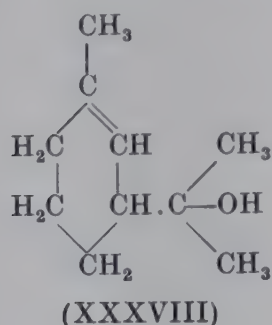


of which had $[\alpha]_D + 108^\circ$ and the other $[\alpha]_D + 49.7^\circ$ (5 per cent. solution in ethyl acetate), the latter acid being present in larger amount. When the structurally isomeric acid (XXXV) of Fisher and Perkin (p. 220) was resolved, it was found to yield an active acid identical in rotation ($[\alpha]_D + 108^\circ$ and -96.6°) with that present in small amount in Perkin and Tattersall's acid. Now the acid having the higher rotation gave on oxidation a *ketonic acid*, which must be formulated as (XXXVI), since, on further treatment with sodium hypobromite, it gave *butane- $\alpha\gamma\epsilon$ -tricarboxylic acid* (XXXVII). It follows, therefore, that the two unsaturated acids have the formulae set out in schemes I and II.

By the methods which have been described already, the optically active acids were converted into the corresponding

alcohols, from which the dihydrochlorides and the active hydrocarbons were prepared.

From the Δ^1 -acid (XXXIV) a *sylveterpineol* (XXXVIII) was obtained, which had b.p. $106-108^\circ/20$ mm., $[\alpha]_D - 48.9^\circ$, whilst the *sylveterpineol* (XXXIX) from the Δ^6 -acid (XXXV) had b.p. $106-107^\circ/20$ mm., $[\alpha]_D + 1^\circ$ and -2.73° .



From the two latter alcohols, which were available in considerable quantity, *d*- and *l*-sylvestrene dihydrochlorides were prepared, which had $[\alpha]_D + 22.5^\circ$ and -21.8° , values in excellent agreement with those found for the dihydrochlorides of sylvestrene from natural sources, $[\alpha]_D + 20.3^\circ$ and -17.1° . When equal quantities of the two dihydrochlorides were mixed the product was found to melt at $52-53^\circ$ and to be identical in all respects with carvestrene dihydrochloride. It was thus conclusively proved that carvestrene was *dl*-sylvestrene.

From the active dihydrochlorides Haworth and Perkin prepared the optically active terpenes by removal of the hydrogen chloride with diethylaniline. The synthetic terpenes had the following constants, which are in good agreement with those found for *d*-sylvestrene quoted on p. 223 although the rotatory power is somewhat lower.

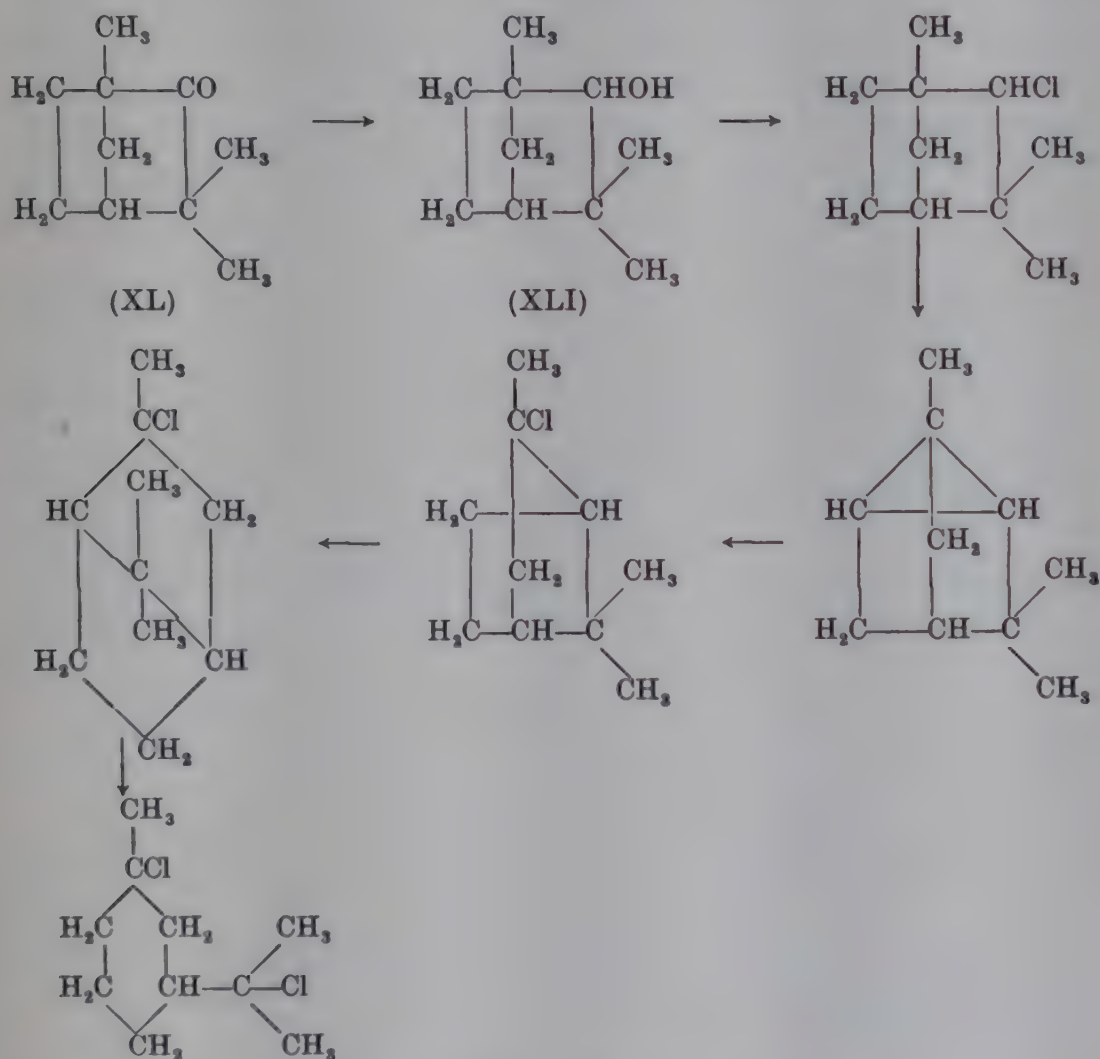
d-Sylvestrene, b.p. $175-178^\circ$, $d^{18}_D 0.8485$, $n_D 1.4572$, $[\alpha]_D + 67.5^\circ$.

l-Sylvestrene, b.p. $176-178^\circ$, $d^{18}_D 0.848$, $n_D 1.4761$, $[\alpha]_D - 68.2^\circ$.

These brilliant investigations prove conclusively that sylvestrene must be regarded as an inseparable mixture of the two hydrocarbons, $\Delta^{1:8(9)}$ -*m*-menthadiene (XXVII) and $\Delta^{6:8(9)}$ -*m*-menthadiene (XXVII a) (p. 222), in which obviously either the one or the other may predominate. This view has been accepted

by Aschan,* who suggests that the characteristic sulphuric acid reaction is only shown by the former.

Reference must be made to a synthesis of carvestrene from fenchone, which was carried out a number of years ago by Kondakov and Schindelmeiser.† When *fenchone* (XL) is reduced it yields the secondary alcohol *fenchyl alcohol* (XLI), from which by prolonged treatment with hydrogen chloride a dihydrochloride, m.p. 49–51°, was obtained. This hydrochloride Kondakov and Schindelmeiser considered to be identical with carvestrene dihydrochloride, since the hydrocarbon prepared therefrom gave the sylvestrene reaction with sulphuric acid. The reactions involved in this synthesis would appear to be somewhat



* *Napthenverbindungen, Terpene und Campherarten*, p. 121.

† *J. pr. Chem.* 1900 [ii], **62**, 8; 1903 [ii], **68**, 108; compare Kondakov, *Parfumerie Moderne*, 1927, **20**, 213.

obscure, but, according to Semmler, they may be formulated in accordance with the scheme* shown on p. 227. A reinvestigation of this synthesis might prove to be of interest.

In the earlier literature, somewhat divergent values have been quoted for the boiling-point and physical constants of sylvestrene, but there can be no doubt that the most accurate are those observed by Haworth, Perkin and Wallach, and given on p. 223, who worked with a large quantity of material. It will be observed that the molecular refraction is normal, as would be anticipated from the constitution.[†] As a rule *d*-sylvestrene is obtained from natural sources, since apparently *l*- Δ^3 - (or Δ^4 -) carene occurs very rarely. According to More,[‡] *l*-sylvestrene dihydrochloride can be obtained from the appropriate fraction of the oil from the oleo-resin *Dacryodes hexandra*, whilst Panicker, Rao and Simonsen[§] obtained this dihydrochloride from the *l*- Δ^3 -carene present in the oil from rhizomes of *Kaempferia galanga*.

The absorption spectrum of *d*-sylvestrene has been studied by Hantzsch,^{||} whilst the X-ray haloes have been described by Vaidyanathan,[¶] using Cu K_α radiation.

Sylvestrene is a very stable hydrocarbon and according to Wallach** it shows no tendency to isomerise when heated in a sealed tube at 250°. It can be most readily characterised by the preparation of the dihydrochloride, m.p. 72–73°. This is probably the *trans*-form, since a liquid dihydrochloride is always obtained at the same time. This dihydrochloride crystallises with great facility and is much more sparingly soluble than the corresponding derivative of dipentene. The racemic form, carvestrene dihydrochloride, melts at 52–53°.

Sylvestrene cannot be reduced with sodium and alcohol,^{††} but according to Sabatier and Murat** it gives *m*-menthane when reduced in hydrogen with a nickel catalyst.

Owing probably to the difficulty in preparing sylvestrene in quantity, no systematic experiments appear to have been carried

* *Die Ätherischen Öle*, vol. II, p. 493. The Wagner rearrangement is assumed to occur with the intermediate formation of a tricyclic hydrocarbon, which is now known to be incorrect.

† Compare Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], **82**, 105.

‡ *J.C.S.* 1899, **75**, 715.

§ *J. Ind. Inst. Sci.* 1926, **9** A, 137.

|| *Ber.* 1912, **45**, 553.

¶ *Indian J. Physics*, 1929, **3**, 387.

** *Annalen*, 1887, **239**, 28.

†† Semmler, *Ber.* 1901, **34**, 3125.

** *Compt. rend.* 1913, **156**, 187.

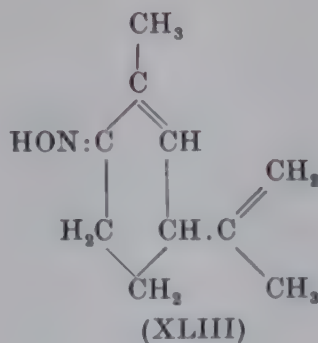
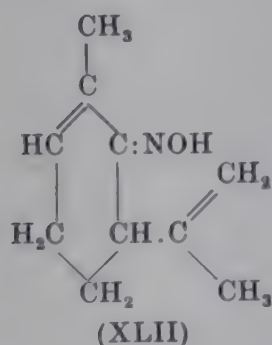
out on its behaviour towards oxidising agents. According to Wienhaus,* on autoxidation sylvestrene yields *sylvecarveols* and *sylvecarvones*, and these on hydrogenation yield *m*-menthane; but full details of this investigation have not appeared. Like α -terpinene, it is readily attacked by chromic acid mixture in the cold, but the products of the reaction have not been examined.

When treated with bromine in acetic acid solution it yields a *tetrabromide*,† m.p. 135–136°, which is strongly dextrorotatory in chloroform solution ($[\alpha]_D + 73.74^\circ$). The corresponding carvestrene derivative does not appear to have been prepared.

Sylvestrene dihydrobromide, like the dihydrochloride, can be readily prepared and has m.p. 72°, $[\alpha]_D + 17.89^\circ$ (in chloroform solution). The corresponding carvestrene derivative was described by Baeyer‡ and has m.p. 48–50°. *Sylvestrene dihydroiodide* melts at 66–67°.

Sylvestrene cannot be hydrated by dilute sulphuric acid; sylveterpineol and sylveterpin have, however, been prepared and are described on pp. 292, 306.

Sylvestrene nitrosochloride, which like limonene nitrosochloride is bimolecular, was prepared by Wallach§ and has m.p. 106–107°. It is dextrorotatory. It does not appear to have been determined whether it exists in *cis*- and *trans*-forms. When the nitrosochloride is treated with alkali it yields, by elimination of hydrogen chloride, a liquid *oxime* which must be represented by either formula (XLII) or (XLIII) or a mixture of the two. From this oxime the ketone, *sylvecarvone*|| has been prepared, but its constitution has not been definitely established (see p. 411).



* *Forh. III. Nord Kemiskmotet*, 1928, p. 211.

† Wallach, *Annalen*, 1885, **230**, 241; 1887, **239**, 29; 1889, **252**, 150.

‡ *Ber.* 1894, **27**, 3490.

§ *Annalen*, 1888, **245**, 272.

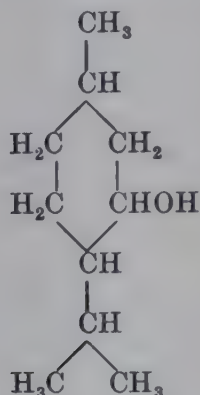
|| Wallach, *ibid.* 1907, **357**, 74.

CHAPTER II

ALCOHOLS

MENTHOL

(*p*-*Menthan*-3-*ol* or 1-*Methyl*-4-*isopropyl*cyclohexan-3-*ol*)



According to Shimoyama* menthol was known in Japan over 2000 years ago, whilst in the west its separation from peppermint oil was noticed by Gambius† in 1771. In addition to the historic interest which the alcohol thus possesses, a study of its chemistry has been of great importance in the development of stereochemistry.

l-Menthol occurs in nature in the so-called peppermint oils, which are obtained from various species of *Mentha piperita* L. It is found mainly in the free state, the percentage of alcohol present in the oils showing considerable variation, dependent upon the habitat. Although natural menthol consists mainly of the crystalline *l*-menthol, it has been shown by Pickard and Littlebury* that the Japanese oil contains in addition a small percentage of the isomeric liquid *d*-neomenthol. It would appear not improbable that with the increase of our knowledge of the stereoisomeric menthols, to which reference will be made in the sequel, other isomerides will be found to occur in nature.

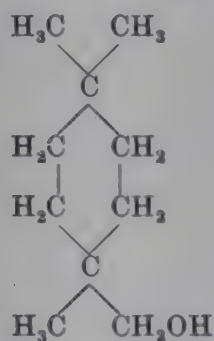
Although menthol has been known for so long, it is only

* Flückiger, *Pharmakognosie des Pflanzenreiches*, 3rd ed., p. 726.

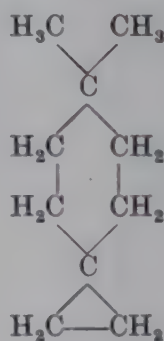
† *Adversariorum varii argumenti, Liber unus*, Leiden, 1771. p. 99.

* *J.C.S.* 1912, 101, 109.

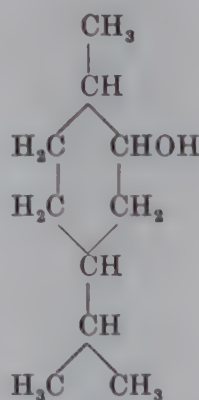
within comparatively recent years that the constitution of the substance has been determined. Prior to the investigations of Oppenheim,* it was known, more especially as the result of the work of Dumas† and Walter,‡ that menthol had the empirical formula $C_{10}H_{20}O$, melted at 34° and boiled at 213.5° ; that it gave on treatment with phosphorus pentoxide a hydrocarbon, $C_{10}H_{18}$, and with phosphorus pentachloride a chloride $C_{10}H_{19}Cl$. Oppenheim recognised that menthol was an alcohol; he prepared from it an *acetate* and *butyrate*, and, by the reduction of the iodide with sodium, a hydrocarbon, which was probably *p*-menthane. Since, on oxidation, it did not yield an aldehyde he concluded that it belonged to Wurtz's so-called "pseudo-alcohol" type. Oppenheim observed also that the alcohol was optically active. The recognition that menthol was an alcohol led Hlasiwetz§ to advance what was probably the first constitutional formula for menthol (I) and the hydrocarbon (II) obtained on dehydration. It is of interest to note that Hlasiwetz formulated menthol as a primary alcohol.



(I)



(II)



(III)

In 1876 Beckett and Wright^{||} made the important observation that menthol could be converted into *p*-cymene, and a few years later Moriya[§] found that when the alcohol was oxidised with chromic acid a ketone, menthone, $C_{10}H_{18}O$, was produced. This led Atkinson to suggest, in a note appended to Moriya's paper, that menthol was a secondary alcohol, derived from the closed

* *Compt. rend.* 1861, **53**, 379; 1863, **57**, 360; *Annalen*, 1861, **120**, 350; 1864, **130**, 176.

† *Annalen*, 1833, **6**, 252; *Ann. chim.* 1832 [ii], **50**, 225.

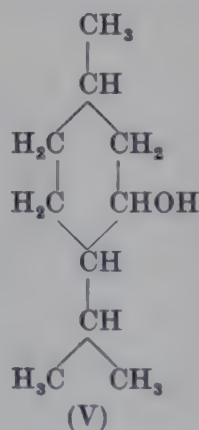
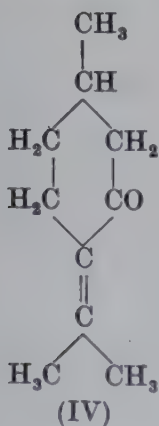
‡ *Compt. rend.* 1836, **6**, 572; *Annalen*, 1838, **28**, 312.

§ *Ber.* 1870, **3**, 539.

^{||} *J.C.S.* 1876, **29**, 1.

¶ *Ibid.* 1881, **39**, 77; Atkinson and Yoshida, *ibid.* 1882, **41**, 49.

chain hydrocarbon formed by the addition of six atoms of hydrogen to ordinary cymene, and that the oxidation product prepared by Moriya was the corresponding ketone. In the years immediately following, menthol was investigated more especially by Arth,* by Leuckart,[†] who prepared a crystalline *phenylurethane*, and by Menschutkin,[‡] who, from a determination of its velocity of esterification, concluded that it was a secondary alcohol, but the next real advance followed from the extensive investigations of menthol and menthone made by Beckmann and his collaborators, the publication of whose results commenced in 1887. One of his students, Mehrländer,[§] suggested that menthol was represented by formula (III) and this was accepted by Brühl,^{||} who, from a consideration of the refractive indices of menthol and a number of its derivatives, concluded that it was a saturated secondary alcohol. This formula was adopted by Beckmann[¶] and Pleissner,** who found that *d*-pulegone gave menthol on reduction. This observation was of considerable importance as, in the following year, Semmler^{††} showed that pulegone must be represented by (IV) (see p. 371) and it followed therefore that since in 1891 Widman had shown that *p*-cymene was 1-methyl-4-isopropylbenzene, in menthol the hydroxy group must be in position (3) and the constitution must be represented by (V).



This constitution for menthol has been fully confirmed by an investigation of the products obtained by the oxidation of the

* *Inter al. Compt. rend.* 1882, **94**, 872; 1883, **97**, 323; 1884, **98**, 576; 1888, **107**, 107.

† *Ber.* 1887, **20**, 114.

‡ *Ann. chim.* 1881 [v], **23**, 14.

§ *Dissertation*, Leipzig, 1887.

|| *Ber.* 1888, **21**, 457.

¶ *Annalen*, 1889, **250**, 350.

** *Ibid.* 1891, **262**, 1.

†† *Ber.* 1892, **25**, 3513.

alcohol itself and of the unsaturated hydrocarbon formed by the elimination of water.

Brunel* prepared a mixture of *dl*-menthols synthetically by the catalytic hydrogenation of thymol by the Sabatier-Senderens process, using a nickel catalyst, and from the mixture of alcohols, he separated a crystalline *dl*-menthol, m.p. 28°. The nature of the products formed in this reaction will be discussed in more detail later, but attention is drawn to the recent work of Barney and Hass† who have developed a large-scale process for the production of *dl*-menthol in high yield from thymol. *dl*-Menthol and optically active menthols have also been synthesised indirectly by the reduction of synthetic menthones, the methods for the preparation of which are described on p. 315.

If the formula for menthol be inspected it will be observed that it contains three asymmetric carbon atoms, and it is capable therefore of existence in four externally compensated and eight optically active forms. Following the suggestion made by Tutin and Kipping,‡ the externally compensated forms may be designated *dl*-menthol, *dl*-neomenthol, *dl*-isomenthol and *dl*-neoisomenthol. Before considering the general properties of menthol, it will be convenient to discuss here the preparation of these various isomerides, and at the same time to consider also the closely related stereoisomeric menthones and menthylamines.

Menthone, containing two asymmetric carbon atoms, is capable of existence in two externally compensated *cis-trans*-modifications (VI) and (VII), each of which should be resolvable into optical enantiomorphs. These *cis-trans*-modifications are designated *dl*-menthone and *dl*-isomenthone, and, for reasons which will be given later, it is very probable that *dl*-menthone has the *trans*-configuration (VII).

The elucidation of the extremely difficult problem of the preparation of the pure stereoisomeric menthols, menthones and menthylamines has been shared by many workers, prominent amongst whom have been Beckmann, Wallach, Pickard, Read and their collaborators. A summary of the early work was given by Kondakov§ and by Read.||

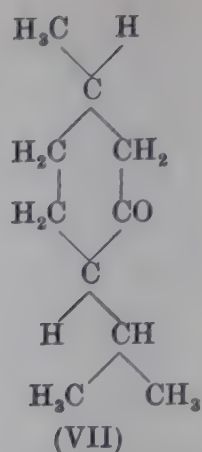
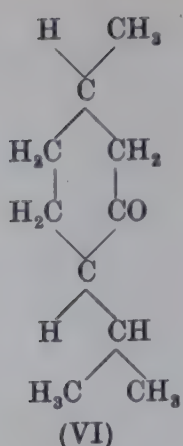
* *Compt. rend.* 1903, **137**, 1268; 1905, **140**, 252.

† *Ind. Eng. Chem.* 1944, **36**, 85.

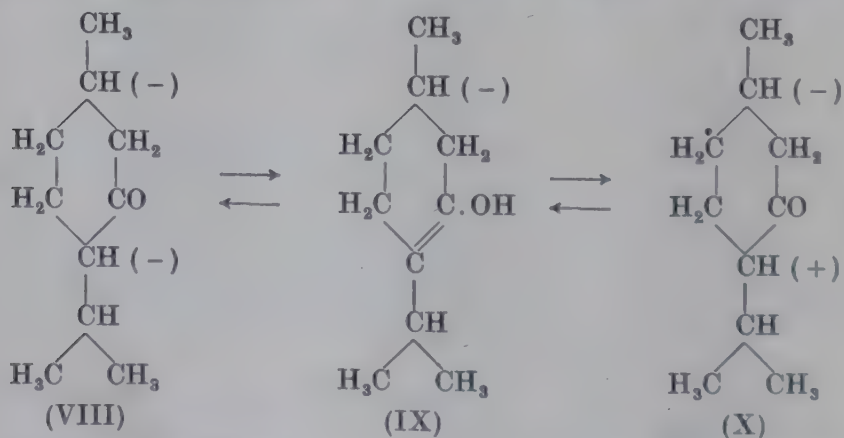
‡ *J.C.S.* 1904, **85**, 67.

§ *J. pr. Chem.* 1905 [ii], **72**, 185.

|| *J.S.C.I.* 1927, **46**, 871; *Chemical Reviews*, 1930, **7**, 1.



The early experiments of Beckmann* on *l*-menthone showed that this ketone was remarkably labile. In his original experiments he used an *l*-menthone, $[\alpha]_D - 28.18^\circ$, which he had prepared by the oxidation of *l*-menthol with chromic acid mixture. He considered this to be pure *l*-menthone and he described the *oxime*, m.p. 58° ($[\alpha]_D - 42.51^\circ$). When this *l*-menthone was dissolved in concentrated sulphuric acid and the mixture poured on to ice, an "inversion" was observed to have occurred and the new ketone was dextrorotatory ($[\alpha]_D + 26.33^\circ$ to $+ 28.14^\circ$). This ketone gave a liquid *oxime* ($[\alpha]_D - 48.5^\circ$). Beckmann recognised that although the optical rotatory powers were of the same order and differed in sign, the two ketones were not optical enantiomorphs, but *cis-trans*-isomerides, the new ketone being designated *d-isomenthone*. The mechanism underlying this inversion has been discussed by Beckmann,[†] by Tutin and Kipping,[‡] and by Gardner, Perkin and Watson.[§] The most probable explanation would appear to be the following. If we



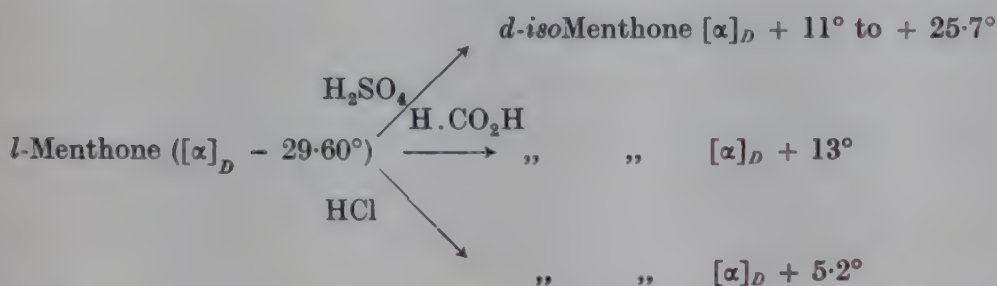
* *Annalen*, 1889, 250, 325.

‡ *J.C.S.* 1904, 85, 65.

† *Pharm. Zeit.* 1903, 48, 780.

§ *Ibid.* 1910, 87, 1760.

assume both the asymmetric carbon atoms (1 and 4) in *l*-menthone (VIII) to be laevorotatory, then, in the first stage of the inversion, the asymmetry of the carbon atom (4) is lost, due to passage into the *enolic* form (IX). When this enol changes back into the ketone this asymmetric carbon atom can become either + or −, so that a mixture of (VIII) and (X), i.e. a mixture of menthone and *isomenthone*, is formed. This hypothesis of the mechanism of the reaction has received support from the investigations of Read and Robertson,* who have shown that the nature of the equilibrium mixture of ketones varies with the “inverting reagent” which is employed. Bell and Caldin,[†] and



also Weissberger,[‡] have recently studied the rate of this inversion under a variety of conditions.

By the reduction of *l*-menthone and *d*-isomenthone Beckmann[§] prepared a mixture of menthols, which he succeeded in partially separating by fractional crystallisation of their benzoates. Complete separation was not possible owing to the complexity of the mixture, and it was obvious that the problem of the preparation of the isomeric menthols and menthones in a state of purity would have to be attacked by a different method.

In the later work there have been three general lines of investigation, which, by their suitable application at various stages, have led to success.

(1) Preparation of the isomeric *dl*-menthols, their resolution and oxidation to the corresponding menthones.^{||}

* *J.C.S.* 1926, p. 2209; compare Gruse and Acree, *J. Amer. C.S.* 1917, **39**, 377; Grossmann and Brauer, *J. pr. Chem.* 1918 [ii], **98**, 9.

† *J.C.S.* 1938, p. 382.

‡ *J. Amer. C.S.* 1943, **65**, 102, 242, 245; Weissberger and Thomas, *ibid.* p. 402.

§ *J. pr. Chem.* 1897 [ii], **55**, 14.

|| In this connection it is important to note that Read and Robertson have shown that the oxidation of a menthol to a menthone with chromic acid mixture under controlled conditions does not cause inversion.

(2) Preparation of the isomeric *dl*-, *d*- and *l*-menthols and menthones by the reduction of unsaturated *dl*-, *d*- and *l*-ketones.

(3) Conversion of the isomeric *dl*-, *d*- and *l*-menthylamine hydrochlorides into the corresponding alcohols by the action of nitrous acid.

It was mentioned above that Brunel, by the catalytic hydrogenation of thymol, obtained a mixture of menthols from which he succeeded in separating, through its crystalline hydrogen phthalate, a *dl*-menthol, m.p. 28°. Pickard and Littlebury* subsequently studied the products of this reduction and showed that, in addition to the mixture of menthols, a *dl*-menthone, *semicarbazone*, m.p. 158°, and a *dl*-isomenthone, *semicarbazone*, m.p. 217°, were formed. By the prolonged fractional crystallisation of the hydrogen phthalates of the mixture of menthols, they succeeded in separating (i) a *dl*-menthol hydrogen phthalate, m.p. 130°, and (ii) a *dl*-menthol hydrogen phthalate, m.p. 177°. From the former, a *dl*-menthol was obtained on hydrolysis which melted at 34° and was characterised by the preparation of the hydrogen succinate, m.p. 85–86°, and the phenylurethane, m.p. 102–104°. By oxidation with chromic acid, a *dl*-menthone was prepared, the oxime of which melted at 80° and the *semicarbazone* at 158°. The same *dl*-menthol hydrogen phthalate was next resolved into its enantiomorphs, *d*-menthol and *l*-menthol hydrogen phthalates. *l*-Menthol hydrogen phthalate showed the characteristic property of crystallising in a labile form, m.p. 110°, and a stable form, prismatic needles, m.p. 122° ($[\alpha]_D - 91.43^\circ$ in chloroform solution). The *l*-menthol, obtained from this phthalate on hydrolysis, melted at 43°, $[\alpha]_D^{19} - 49.44^\circ$, and was identical in all respects with natural *l*-menthol. This gave on oxidation an *l*-menthone, $[\alpha]_D - 29.18^\circ$, *semicarbazone*, m.p. 189°. The corresponding *d*-menthol was also prepared and was characterised by the preparation of the benzoate, m.p. 56°, $[\alpha]_D + 90.72^\circ$.

From the *dl*-menthol hydrogen phthalate, m.p. 177°, the corresponding alcohol was next prepared; this was designated *dl*-neomenthol† and it melted at 51°; it was characterised by

* *J.C.S.* 1912, 101, 109.

† This was probably identical with the hydrogen phthalate of the alcohol obtained by Enklaar (*Ber.* 1908, 41, 2086) by the cyclisation of geraniol and also with that originally described by Beckmann (*J. pr. Chem.* 1897 [ii], 55, 30).

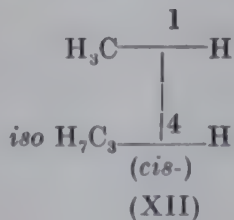
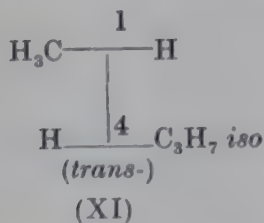
the preparation of the *hydrogen succinate*, m.p. 67–68°, and the *phenylurethane*, m.p. 114°. The enantiomorphic forms of the alcohol were oils, *d*-neomenthol, b.p. 98°/16 mm., $[\alpha]_D + 19.69^\circ$, and *l*-neo-menthol, b.p. 105°/21 mm., $d_{40}^{20} 0.8995$, $n_D^{20} 1.4603$, $[\alpha]_D^{29.5} - 19.72^\circ$. The *d*-hydrogen phthalate melted at 142–144° ($[\alpha]_D + 62.66^\circ$ in acetic acid), the *l*-hydrogen succinate melted at 68° and the *l*-phenylurethane at 107–108°.

The oxidation of *dl*-neomenthol gave *dl*-menthone, whilst from the active forms, *d*- and *l*-neomenthols, *l*-menthone, b.p. 204°/750 mm., $[\alpha]_D^{19} - 23.3^\circ$, semicarbazone, m.p. 187°, and *d*-menthone, b.p. 204°/750 mm., $d_{18}^{18} 0.895$, $[\alpha]_D + 24.85^\circ$, semicarbazone, m.p. 187°, respectively, were prepared.

Later, Vavon and Couderc* showed that *d*-neomenthol could be prepared more conveniently by the hydrogenation of *l*-menthone in the presence of platinum black. When purified through its hydrogen succinate, these authors observed the rotation $[\alpha]_{578} + 21.95^\circ$. Read and Grubb† have obtained *d*-neomenthol by the reduction of *l*-menthone with aluminium isopropoxide.

As the result of these very elegant investigations two *dl*-“menthols”, together with their optical enantiomorphs, were known in a state of purity. Further, it had been shown that both menthol and neomenthol gave on oxidation the same menthone, the laevorotatory form being identical with natural *l*-menthone. The next problem requiring consideration involved the configuration of these two menthols and the derived menthone. It will be convenient to deal with this before proceeding to a review of the methods which have led to the preparation of *dl*-isomenthone and the corresponding alcohols.

It had been assumed that natural *l*-menthone had the *cis*-configuration, the inversion product, *d*-isomenthone, being regarded as the *trans*-modification. These two forms may be represented by the outline formulae (XI) and (XII). It was then



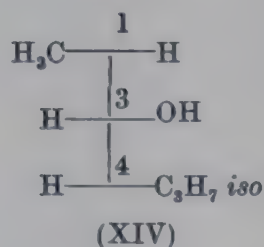
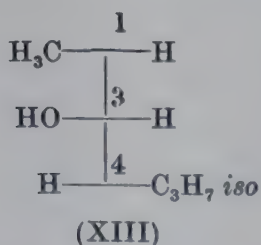
* *Compt. rend.* 1924, 179, 405.

† *J.S.C.I.* 1934, 53, 52 T.

suggested by Zeitschel and Schmidt* that this assumption was incorrect, and that actually *l*-menthone possessed the *trans*-configuration (XI) and *d*-isomenthone the *cis*- (XII).

According to the Auwers-Skita† rule, a substance possessing a *cis*-configuration always has a higher density and refractive index than its *trans*-isomeride. If this be the case, then menthone must have the *trans*-configuration. This view is in accord also with the determination of the parachor values of the two ketones which has been made by Carter,‡ and further support has been provided by Keats§ who has prepared two different *p*-menthanes by the electrolytic reduction of menthone and isomenthone respectively. The physical constants of these products indicate a *trans*-configuration for the hydrocarbon derived from menthone. On the present evidence therefore it is justifiable to represent *dl*-, *d*- and *l*-menthones by formula (XI) and *dl*-, *d*- and *l*-isomenthones by (XII).

A problem of greater complexity arises in attempting to decide the configuration of the alcohols. Each of the ketones can give rise to six alcohols (two externally compensated and four optically active); of these, menthol and *neomenthol* correspond to the *trans*-ketone (XI), and the question which arises is, what is the position of the hydrogen atom and hydroxyl group attached to the new asymmetric carbon atom? The two possible configurations may be represented by (XIII) and (XIV).



Vavon and Couderc,|| from observations on the rate of esterification of *l*-menthol and *d*-*neomenthol*, concluded that in *d*-*neomenthol* the hydroxyl group (3) occupied the *cis*-position in respect to the *isopropyl* group (4), since *d*-*neomenthol* esterifies less readily than *l*-menthol. This view was adversely criticised

* Ber. 1926, 59, 2298.

† Annalen, 1915, 410, 287; 1920, 420, 91.

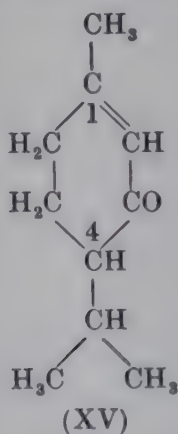
‡ J.C.S. 1937, p. 2003.

* J.C.S. 1927, p. 1278.

|| Compt. rend., 1924, 179, 405.

by Zeitschel and Schmidt,* since a comparative study of the action of phosphorus pentoxide, phosphorus pentachloride, formic acid and thionyl chloride on the two alcohols had shown that, whereas *d*-neomenthol gave in all cases a good yield of the hydrocarbon, *l*-menthol behaved very differently. With formic acid *l*-menthol gave the ester in a yield of 94 per cent., with phosphorus pentachloride *l*-menthyl chloride was obtained, whilst it did not react at all with thionyl chloride. At the time, it was thought that the elimination of water between the hydroxyl (3) and the hydrogen (4) would occur most readily when these groups were in close proximity; Zeitschel and Schmidt therefore favoured structure (XIII) for *d*-neomenthol. The subsequent realisation of the frequent occurrence of *trans*-elimination in such reactions, considered in conjunction with the careful work of Read and Grubb† (see p. 241), which confirms the observations of Vavon and Couderc, leads to the conclusion that *dl*-, *d*- and *l*-menthols are represented by (XIII), and *dl*-*d*- and *l*-neomenthols by (XIV). It is obvious that both these alcohols must on oxidation give the same *trans*-ketone (XI).

A mixture of stereoisomeric menthols and menthones may be prepared by the reduction, either catalytically or with sodium and alcohol, of various unsaturated ketones. In 1921 Read and his collaborators commenced a detailed study of the properties of the menthones and menthols which are formed when *dl*-, *d*- and *l*-piperitones (Δ^1 -*p*-menthen-3-one) (XV) are reduced.



In this ketone the optical activity is associated with the asymmetry of the carbon atom (4), and reduction of the ethylenic

* Ber. 1926, 59, 2298.

† J.C.S. 1934, p. 1779.

linkage, with the consequent introduction of asymmetry at carbon atom (1) also, must lead to the formation of a mixture of isomeric menthones, and it seemed that it might prove possible to separate *isomenthone* from this mixture in a state of purity.

A study* of the catalytic hydrogenation of *d*- and *l*-piperitones and of *l*- Δ^4 -*p*-menthen-3-one in the presence of a palladium catalyst showed that a menthone was formed with a rotatory power opposite in sign from that of the parent ketone. *d*-Pulegone, also, gave a product which consisted mainly of *d*-*isomenthone*.

			$[\alpha]_D^{15}$ (unsaturated ketone)	$[\alpha]_D^{15}$ (saturated ketone)
<i>d</i> -Piperitone	+ 62.50°	- 71.41°
<i>l</i> -Piperitone	- 53.90°	+ 69.10°
<i>d</i> -Pulegone	+ 23.60°	+ 33.45°
<i>l</i> - Δ^4 - <i>p</i> -Menthen-3-one	- 78.36°	+ 43.24°

Although the *isomenthones* obtained from *d*- and *l*-piperitones were, from their rotatory powers, obviously of a higher degree of purity than that prepared by the inversion of *l*-menthone, yet they were by no means pure. Purification through derivatives, such as the semicarbazones, was not feasible since the regeneration of the pure ketone would, owing to the tendency to inversion, be impossible. It was necessary therefore to carry out the purification through the corresponding alcohols, which could be prepared in a state of purity by the application of one or more of the following methods: (i) fractionation of the hydrogen phthalate, (ii) fractional esterification, (iii) fractional saponification of esters, and (iv) the action of nitrous acid on the pure crystalline menthylamine hydrochlorides. The bases required for the last method were obtained either by distillation of the ketone with ammonium formate† or by reduction of the oxime with sodium and alcohol.‡

When the liquid oxime of the crude *d*-*isomenthone* from *l*-piperitone was reduced with sodium and alcohol a mixture of

* *Inter al.*, Read and Cook, *J.C.S.* 1925, 127, 2782; Read and Robertson, *ibid.* 1926, p. 2209; Read, Cook and Shannon, *ibid.* p. 2223; 1927, p. 1276; compare Skita and Ritter, *Ber.* 1910, 43, 3394; Wallach, *Annalen*, 1913, 397, 218; Hüchel and Wagner, *Ber.* 1941, 74, 657.

† Wallach, *Annalen*, 1893, 276, 296.

‡ Andres and Andreef, *Ber.* 1892, 25, 617.

menthylamines was obtained from which, on fractional crystallisation of the hydrochlorides a pure product was readily separated and characterised. This menthylamine hydrochloride ($[\alpha]_D + 23.6^\circ$) was designated *d-isomenthylamine hydrochloride* and gave on treatment with nitrous acid *d-isomenthol*, $[\alpha]_D + 27^\circ$, which was identical with the menthol described previously by Beckmann* and Zeitschel and Schmidt.† From this alcohol *d-isomenthone* was prepared, which had $[\alpha]_D + 91.7^\circ$. This *isomenthone* gives a liquid oxime and the *semicarbazone* is unsuitable for its characterisation, which is best effected by the preparation of the *hydrochloride* of the oxime, m.p. 132° , $[\alpha]_D + 38.6^\circ$, in chloroform.

From *dl*-piperitone, *dl-isomenthylamine hydrochloride*, *dl-isomenthol*, and *dl-isomenthone* were prepared in a similar manner. With the exception, therefore, of *l-isomenthone*,‡ which has not yet been obtained free from isomerides, all the menthones are now known in a pure state,§ and their properties may be conveniently summarised.

	M.p.	B.p.	<i>d</i>	n_D^{20}	$[\alpha]_D$	M.p. <i>semicarbazone</i>	M.p. <i>oxime</i>	M.p. <i>oxime</i> <i>hydrochloride</i>
<i>dl</i> -Menthone	—	204°/750 mm.	—	—	$\pm 0^\circ$	{ α 185–186° β 161°}	81–82°	—
<i>d</i> -Menthone	—	204°/750 mm.	—	—	+24.85°	187°	59°	—
<i>l</i> -Menthone	–6°	204°/750 mm.	0.8946	1.4504	–29.60°	187°	59°	118–119°
<i>dl</i> -iso-Menthone	—	90–93°/18 mm.	—	—	$\pm 0^\circ$	{ α 225° β 177–178°}	99–100°	127–128°
<i>d</i> -iso-Menthone	–35°	86–87°/13 mm.	0.9000	1.4530	+95°	264°	Oil	132°

The *neoisomenthols* proved to be the most difficult to obtain, but eventually it was discovered by Read and Grubb|| that the hydrogenation of *l*- and *dl*-piperitone below 100° led to the formation of products which, when rigorously purified through the hydrogen phthalates, the phosphoric acid compounds,¶ and the *p*-nitrobenzoates, gave pure *d*- and *dl*-*neoisomenthol*, respec-

* Ber. 1909, 42, 846.

† Ibid. 1926, 59, 2298.

‡ The preparation of *l-isomenthone* of 91 per cent. purity has been reported by Hiraidzumi, Chem. Zentr. 1931, 1, 1277.

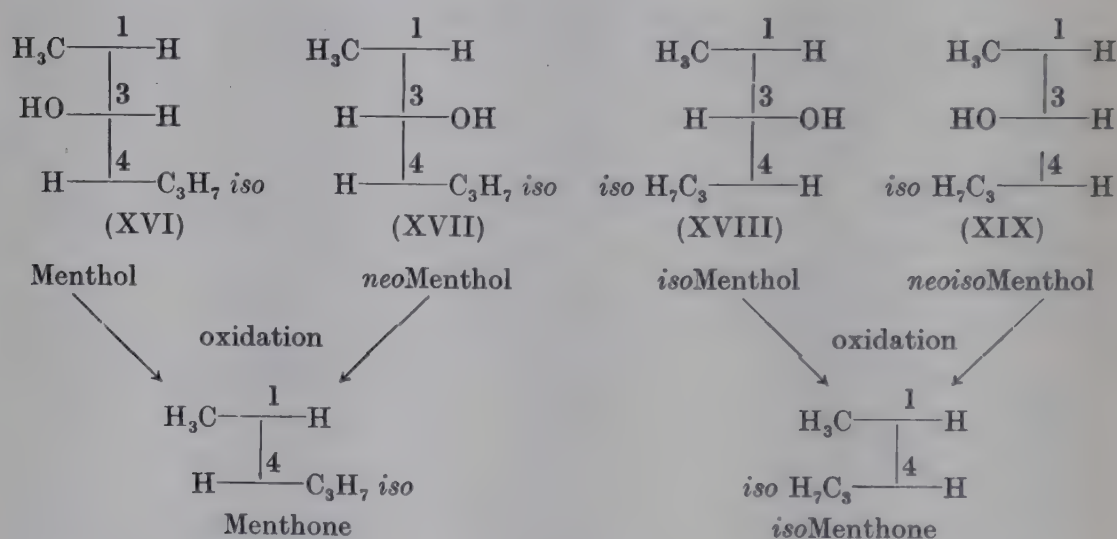
§ Compare Rupe and Gassmann, Helv. Chim. Acta, 1929, 12, 193; 1934, 17, 283.

|| J.C.S. 1934, p. 313; compare Schmidt and Schülz, Schimmel's Report, 1935, p. 93; Hückel and Niggemeyer, Ber. 1939, 72, 1354.

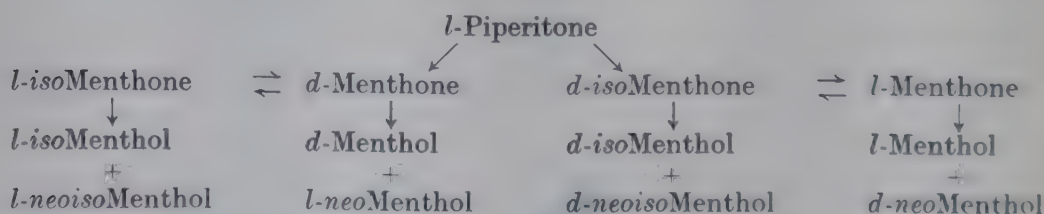
¶ Blagden and Huggett, J.C.S. 1934, p. 317.

tively. *Neoisomenthol*, like *neomenthol*, very readily loses water by *trans*-elimination to yield Δ^3 -*p*-menthene.

Read and Grubb were now in a position to determine the relative reactivities of all the possible "menthols", and it was found* that the comparative reaction velocities with *p*-nitrobenzoyl chloride under standard conditions were: menthols, 16.5; *isomenthols*, 12.3; *neoisomenthols*, 3.1; *neomenthols*, 1.0. Assuming that these variations are due to steric hindrance, the relative molecular configurations must be as shown by the formulae (XVI)–(XIX). These conclusions are in agreement also with the Auwers-Skita rule, since the compounds (XVIII) and (XIX), in which the hydrogen atoms at position (1) and (4) are in the *cis*-position to each other, possess higher densities and refractive indices than (XVI) and (XVII). The constants of these alcohols, together with those of some of their derivatives, are given in the table on page 243.



The scheme below indicates how all the optically active menthols are related to *l*-piperitone.[†]



* *J.C.S.* 1934, p. 1779.

[†] Read, *Nineteenth Streatfeild Memorial Lecture*, Royal Institute of Chemistry, 1936.

	M.p.	B.p.	d_{15}^{16}	n_D^{20}	$[\alpha]_D$	M.p. Phenyl- urethane
<i>dl</i> -Menthol	38°	216°	0.904	1.4615	$\pm 0^\circ$	102–104°
<i>l</i> -Menthol	43°	216°	0.904	1.4609	-49.4°	112°
<i>dl</i> - <i>neo</i> Menthol	53°	212°	0.903	1.4604	$\pm 0^\circ$	114°
<i>d</i> - <i>neo</i> Menthol	–22°	212°	0.903	1.4603	$+19.7^\circ$	107–108°
<i>dl</i> - <i>iso</i> Menthol	53.5°	219°	—	—	$\pm 0^\circ$	—
<i>d</i> - <i>iso</i> Menthol	82.5°	219°	—	—	$+27.0^\circ$ ¹	—
<i>dl</i> - <i>neoiso</i> Menthol	14°	215°	—	1.4649	$\pm 0^\circ$	—
<i>d</i> - <i>neoiso</i> Menthol	–8°	215°	0.913 ²	1.4649	$+0.14^\circ$	—

	M.p. Hydrogen phthalate	M.p. <i>p</i> -Nitro- benzoate	M.p. 3:5- Dinitro- benzoate	M.p. Phosphoric acid compound	M.p. <i>d</i> -Camphor 10-Sulphonate	M.p. <i>l</i> -Camphor 10-Sulphonate
<i>dl</i> -Menthol	130°	91°	121°	74°	—	—
<i>l</i> -Menthol	122°	61–62°	153°	74°	125.5°	47°
<i>dl</i> - <i>neo</i> Menthol	177°	78.5°	130°	86°	—	—
<i>d</i> - <i>neo</i> Menthol	142–144°	95°	153°	86°	116°	92°
<i>dl</i> - <i>iso</i> Menthol	107–108°	64.5°	130°	46°	—	—
<i>d</i> - <i>iso</i> Menthol	107–108.5°	54°	147°	—	30–31°	33–34°
<i>dl</i> - <i>neoiso</i> Menthol	—	63–64°	73°	—	—	—
<i>d</i> - <i>neoiso</i> Menthol	—	73°	101°	60°	69–70°	84–86°

¹ In alcohol.² d_4^{18} .

It must be emphasised that the prefixes *d*- and *l*- refer to the optical rotatory power of each substance and therefore do not indicate the relative configurations. Thus, *l*-menthol is configurationally related to *d*-*iso*, *d*-*neo*, and *d*-*neoiso*menthols. It would appear that a stage has now been reached when it would be advantageous to remedy this defect, particularly in view of the fact that “*d*”-*neoiso*menthol, although dextrorotatory in alcohol, is laevorotatory in ether or chloroform.*

Resolution of the *dl*-menthols has been accomplished by formation of the glucoside,[†] the mandelate,[‡] or the tartranilic ester,[§] and by feeding the alcohol to rabbits, when a preponderance of the *d*-menthylglucuronoside may be isolated from the urine.^{||} For large-scale preparation, the best processes are those developed by Read and his collaborators.[¶] These are of particular interest, because the only optically active material required is a small quantity of *l*-menthol; this is converted into *l*-menthoxyacetic acid or into *l*-menthylglycine, either of which

* Hückel and Niggemeyer, *Ber.* 1939, **72**, 1354.† Neuberg, *Fermentforschung*, 1928–1929, **10**, 491.‡ McKenzie and Luis, *J.C.S.* 1934, p. 715.§ Barrow and Atkinson, *J.C.S.* 1939, p. 638.|| Williams, *Biochem. J.* 1938, **32**, 1849; 1939, **33**, 1519; 1940, **34**, 48.¶ Read and Grubb, *J.S.C.I.* 1932, **51**, 329 T; *J.C.S.* 1933, p. 167; Clark and Read, *J.C.S.* 1934, p. 1776.

may then be employed in the usual way for the resolution. The whole process thus becomes continuous, so that indefinitely large quantities of *dl*-menthol may be resolved into the pure *d*- and *l*-forms.

It may be convenient to consider here very briefly the isomeric menthylamines, which have been prepared by either of the methods mentioned above. An *l*-menthylamine was first prepared by Andres and Andreef* from *l*-menthoneoxime, whilst, almost at the same time, Wallach† prepared the same substance from *l*-menthone by heating with ammonium formate. He obtained in addition a dextrorotatory amine, *R*-menthylamine. He recognised that although it was opposite in sign it was not the optical enantiomorph of *l*-menthylamine, since whereas *l*-menthylamine hydrochloride gives with nitrous acid *l*-menthol, *R*-menthylamine hydrochloride yields mainly a racemic Δ^3 -*p*-menthene. He naturally, though erroneously, deduced therefore that in the *R*-base the NH_2 group and the H atom were in close proximity. In 1904 Tutin and Kipping by the reduction of an "*l*-menthoneoxime" (actually a mixture of the oximes of *l*-menthone and *d*-isomenthone) prepared four menthylamines, which were characterised by the preparation of a number of derivatives, but it is probable that not all of the products were stereochemical individuals. In 1913 Wallach‡ obtained from *dl*-menthoneoxime an *i*-menthylamine, which was not homogeneous, being derived from both menthoneoxime and isomenthoneoxime. With both *dl*-menthone and *dl*-isomenthone now available, it has proved possible to prepare and characterise the majority of the menthylamines and to assign to them their configurations. Without entering into details of the methods employed, for which reference should be made to the recent memoirs of Read and his collaborators, it will suffice to give a table of the observed data,^s the configurations of the amines being represented by formulae (XX), (XXI), (XXII) and (XXIII).

* *Ber.* 1892, 25, 617.

† *Annalen*, 1893, 276, 296.

‡ *Ibid.* 1913, 397, 218.

^s Read, Cook and Shannon, *J.C.S.*, 1926, p. 2225; Read and Robertson, *ibid.* 1927, p. 2168; Read, *Chem. Reviews*, 1930, 7, 21; Read and Storey, *J.C.S.* 1930, p. 2761; Read and Grubb, *ibid.* 1934, p. 1779. See also Vavon and Chilouet, *Compt. rend.* 1936, 203, 1526; Read and Hendry, *Ber.* 1938, 71, 2544.

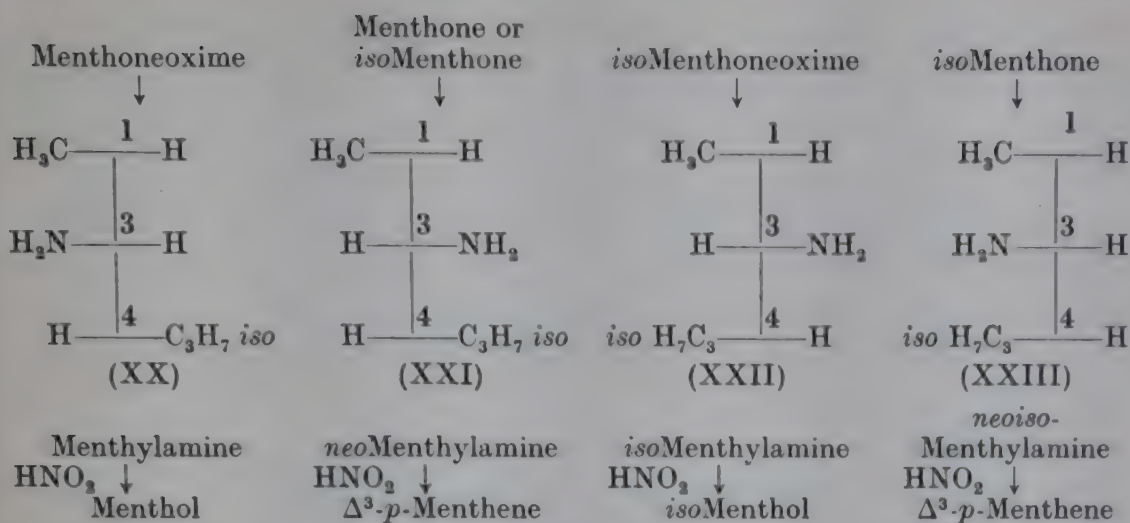


Table of Physical Constants of the Menthylamines

	<i>l</i> -Menthylamine	<i>d-neo</i> -Menthylamine	<i>d-iso</i> -Menthylamine	<i>d-neoiso</i> -Menthylamine
b.p.	81–82°/12 mm.	84°/13 mm.	87°/13.5 mm.	89°/14.5 mm.
d_4^{25}	0.8525	0.8551	0.8632	0.8636
n_D^{25}	1.4600	1.4614	1.4659	1.4670
$[\alpha]_D^{25}$	– 44.5°	+ 15.1°	+ 29.0°	+ 2.3°

Table of Melting Points and Rotatory Powers of Menthylamine Derivatives¹

Derivative	Menthylamines		<i>neo</i> Menthylamines		<i>iso</i> Menthylamines		<i>neoiso</i> -Menthylamine
	<i>dl</i> -	<i>l</i> -	<i>dl</i> -	<i>d</i> -	<i>dl</i> -	<i>d</i> -	<i>d</i> -
Hydrochloride	>250°	>280° ² –36.6° ³	184–185°	189° +21.5°	>250°	>250° +23.6°	>250° +20.9°
Formyl	77–78°	102–103° ² –83.8° ²	86°	117–118° +53.8°	45–47°	45–46° +31.3°	Liquid –3.9°
Acetyl	123–124°	145° ² –81.7° ²	160–161°	169–170° +53.0°	Liquid	77–79° +30.7°	99–100° –2.6°
Benzoyl	145–146°	157° –62.8°	101–102°	121.5° +22.7°	127–128°	97–98° +18.3°	151° –10.4°
3-Naphthalene-sulphonyl	145–146°	135° –53.3°	209–210°	208° +43.7°	141–142°	80–81° –2.8°	120° –10.7°
Benzylidene	Liquid	60–70° –132.5°	Liquid	45–46° +61.7°	41–44°	67–68° +90.7°	68–69° –34.2°
Salicylidene	Liquid	57–58° –119.2°	69.5°	99–100° +30.0°	95°	122° +77.6°	99–100° –17.9°
Carbamide	157°	134–136° ²	162–163°	155–156° ²	203–204°	141.5–142.5° +29.0°	115–116° –3.1°
Phenylcarbamide	162°	140–141° ²	183–184°	177–178° ²	142–143°	142° +21.8°	149–150° –12.1°
Phenylthio-carbamide	151°	135° ³	169–170°	178–179° ³	137°	114.5–115.5° +46.7°	99° –6.7°

¹ The values of $[\alpha]_D$, denoted by the prefixed + or – signs, were observed in water for the hydrochlorides and in chloroform for the remaining derivatives. It is worthy of note that *neoisomenthylamine* derivatives are frequently laevorotatory.

² Wallach, *Annalen*, 1893, 276, 306; 1898, 300, 278. ³ Tutin and Kipping, *J.C.S.* 1904, 85, 65.

dl-Menthol can exist in either of two crystalline modifications, which have melting-points of 28° and 38° respectively, whilst *l*-menthol crystallises in four different forms which have been studied by Schaum* and by Wright.† The stable, α -form, consists of broad needles, which show dextrorotatory polarisation, although the melt is laevorotatory. The absorption spectrum of menthol in the ultra-violet has been examined by Purvis,‡ but it shows no point of special interest. The X-ray structure has been studied by Sidhu.§

Reference has been made above to all the more general methods which may be used for the preparation of menthol. In considering the properties of this substance, it must be borne in mind that the majority of the reactions described have been carried out with natural *l*-menthol. In the sequel it will be assumed that this substance has been used unless the contrary is stated.

Reduction of menthol with hydriodic acid and red phosphorus gives *p*-menthane,^{||} but conversion into this hydrocarbon can be effected more conveniently by reduction of menthyl chloride. According to Komatsu and Kurata[¶] *l*-menthol, when passed over reduced copper in a current of hydrogen at about 300°, gives a mixture of *p*-menthane, menthone, thymol and *p*-cymene, whilst Neave** observed only the formation of *p*-menthane; the divergence in the results arises probably from a slight difference in the surfaces of the catalysts used.

On oxidation of *l*-menthol with chromic acid mixture it is converted almost quantitatively into *l*-menthone,^{††} practically no inversion occurring. If, however, the oxidation is carried out with chromic acid in acetic acid solution^{‡‡} degradation occurs with formation of β -methyl- δ -isobutyryl-*n*-valeric acid (XXIV). This acid, which is an oil, b.p. 186–187°/30 mm., *oxime*, m.p. 98.5°, is also formed by the action of alkali on *bis*-nitrosomenthone (XXV)^{§§} (see p. 321).

* *Annalen*, 1899, **308**, 39.

† *J. Amer. C.S.* 1917, **39**, 1515; see also Huggett, *Quart. J. Pharm.* 1942, **15**, 218. The stereochemical relationships given in the latter paper are obviously erroneous.

‡ *J.C.S.* 1924, **125**, 415.

§ *J. App. Physics*, 1939, **10**, 83.

|| Berthelot, *Bull. Soc. chim.* 1869 [ii], **11**, 102; Berkenheim, *Ber.* 1892, **25**, 688.

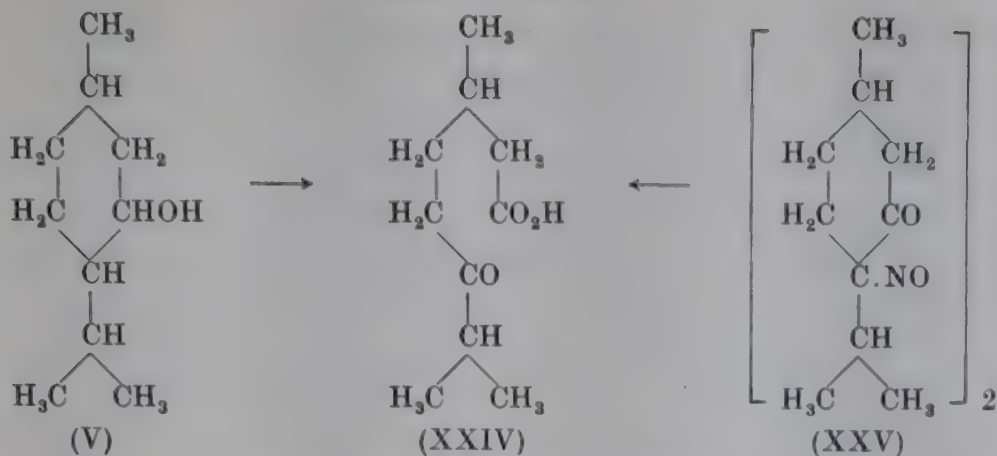
¶ *Mem. Coll. Sci. Kyoto*, 1925, **8**, 35.

** *J.C.S.* 1912, **101**, 514.

†† Beckmann, *Annalen*, 1889, **250**, 329.

‡‡ *Ibid.*

§§ Baeyer and Manasse, *Ber.* 1894, **27**, 1914.



By the oxidation of the alcohol with potassium permanganate in acid solution, Arth* obtained a mixture of formic, acetic, propionic, butyric and oxalic acids, together with the ketonic acid (XXIV). He also isolated an acid which he called γ -pimelic acid; the actual constitution of this acid, m.p. 86–87.5°, is not known but it is probably β -methyladipic acid.

With bromine, menthol gives liquid products which have not been identified. Treatment with halogen acids leads to replacement of the hydroxyl group by halogen, but the products are probably not quite homogeneous since, during the reaction, it is not unlikely that elimination, with subsequent readdition of the halogen acid, occurs. According to Hückel and Pietrzok† the products usually contain *neomenthyl* chloride. The preparation of *l*-3-chloro-*p*-menthane (menthyl chloride) can be effected much more conveniently by the action of phosphorus pentachloride, which, as was observed by Zeitschel and Schmidt,‡ gives with *l*-menthol almost entirely the chloride, although *d*-*neomenthol* is mainly dehydrated to *d*- Δ^3 -*p*-menthene under similar conditions. This chloride, which has been frequently described,[§] is an oil, b.p. 87.5–90°/13 mm., and it is somewhat unstable, passing readily into Δ^2 - and Δ^3 -*p*-menthenes.^{||} Although some doubt has been expressed as to whether this is the true 3-chloro-derivative, the experiments of Kursanov[¶] would appear

* *Ann. Chim.* 1886 [vi], 7, 433.

† *Annalen*, 1939, 540, 250; see also Hückel and Kümmerle, *Ber.* 1942, 75, 115.

‡ *Ber.* 1926, 59, 2298.

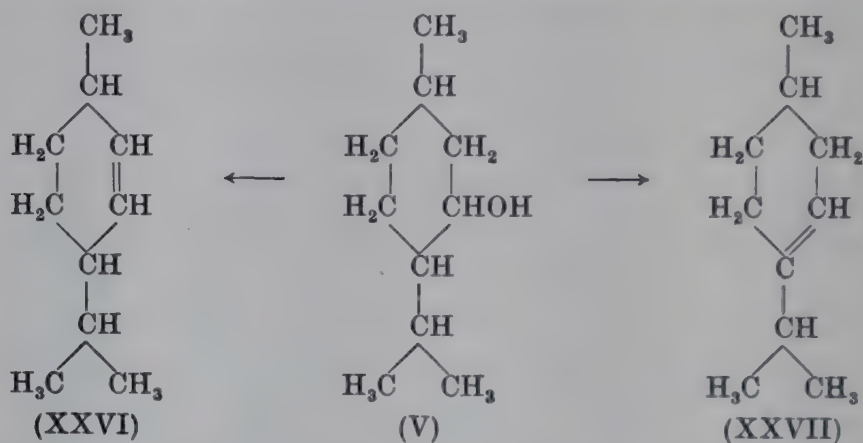
§ Berkenheim, *Ber.* 1892, 25, 686; Kondakov, *ibid.* 1895, 28, 1618; Kondakov and Lutschinin, *J. pr. Chem.* 1899 [ii], 60, 257; Kursanov, *J. Russ. Phys. Chem. Soc.* 1901, 33, 289; Norris and Mulliken, *J. Amer. C.S.* 1920, 42, 2097.

|| Hückel and Pietrzok, *Annalen*, 1940, 543, 230.

¶ *J. Russ. Phys. Chem. Soc.* 1914, 46, 815; 1916, 48, 867.

to leave no doubt as to this being the case, since he has reconverted it into an *l*-menthol identical with the product from which it was prepared. When the alcohol is treated with phosphorus trichloride, in addition to menthyl chloride, *l*-trimenthyl phosphite $P(OC_{10}H_{19})_3$, m.p. $44-45^\circ$, $[\alpha]_D -30^\circ$, is formed, whilst with phosphorus oxychloride *trimenthyl phosphate*, m.p. 86° , can be prepared.* By the action of phosphorus pentabromide *l*-menthylbromide, b.p. $100-103^\circ/13\text{ mm.}$, $[\alpha]_D -9.68^\circ$, is formed.†

On dehydration menthol can theoretically yield two hydrocarbons, Δ^2 -*p*-menthene (XXVI) and Δ^3 -*p*-menthene (XXVII), but it has been shown by an investigation of the degradation products that the menthene so obtained is generally the Δ^3 -



isomeride. In only one case apparently, namely by the use of boric anhydride, would the product appear to be mainly the Δ^2 -isomeride.‡

This hydrocarbon (Δ^3 -*p*-menthene) was probably first prepared by Walter§ by the action of phosphoric anhydride on *l*-menthol and has since been frequently investigated. Probably the purest specimen so far obtained was that prepared by Tschugaev|| by the distillation of *methyl l*-menthylxanthate, the rotatory power of the hydrocarbon being $[\alpha]_D +140.77^\circ$. According to Senderens¶ the hydrocarbon can be obtained in

* Milobedski and Kolutowski, *Rocz. Chem.* 1926, **6**, 67.

† Kondakov, *Ber.* 1895, **28**, 1620; Kondakov and Schindelmeiser, *J. pr. Chem.* 1903 [ii], **67**, 193.

‡ Mereshkovski, *J. Russ. Phys. Chem. Soc.* 1913, **45**, 1686.

§ *Compt. rend.* 1836, **6**, 572; *Annalen*, 1838, **28**, 312.

|| *Ber.* 1899, **32**, 3332; compare McAlpine, *J.C.S.* 1932, p. 912; Malcolm and Read, *ibid.* 1939, p. 1037.

¶ *Compt. rend.* 1912, **154**, 1170; compare Beckmann, *Annalen*, 1889, **250**, 358.

a yield of over 90 per cent. by the action of very dilute sulphuric acid (1–2 per cent.) on *l*-menthol. As has been pointed out elsewhere, the dehydration of the isomeric menthols does not proceed with equal facility. Δ^3 -*p*-Menthene, on oxidation with selenium dioxide, gives a mixture of Δ^3 -*p*-menthene-2-one and Δ^3 -*p*-menthen-5-one.*

Δ^2 -*p*-Menthene may be obtained indirectly from menthol by treatment of the *p*-toluenesulphonate with alkali.† *trans*- Δ^2 -*p*-Menthene has b.p. 55.5°/16 mm., $[\alpha]_D + 132.1^\circ$, and the *cis*-form has b.p. 46–48°/10 mm., $[\alpha]_D + 45.2^\circ$. The oxidation of this hydrocarbon with lead tetra-acetate has been shown by Hückel and Kummerle‡ to give a menthane-2:3-diol and a *p*-menthenol. The stereochemical characterisation of the *p*-menthenols has been initiated by Malcolm and Read.§

Since *l*-menthol is readily accessible in a high state of purity it has been employed largely in the study of the influence of constitution on optical rotatory power. Prominent in this field have been Frankland, Cohen, McKenzie, Rupe, Patterson and Lowry, to whose original memoirs reference should be made for details of the work. The majority of the substances studied have been the menthyl esters of organic acids, of which an extremely large number have been described. *l*-Menthyl *N*-aminocarbamate is a valuable reagent for the resolution of carbonyl compounds.|| Menthol *glucosides* were prepared by Fischer and his collaborators.¶

Owing to its being a mild antiseptic, menthol finds numerous applications in medicine and pharmacy.

* Borgwardt and Schwenk, *J. Amer. C.S.* 1934, **56**, 1185.

† Hückel, Tappe and Legutke, *Annalen*, 1940, **543**, 191; Hückel and Wagner, *Ber.* 1941, **74**, 657.

‡ *J. pr. Chem.* 1942 [ii], **160**, 74.

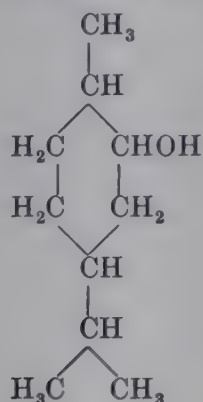
§ *J.C.S.* 1939, p. 1037.

|| Woodward, Kohmann and Harris, *J. Amer. C.S.* 1941, **63**, 120.

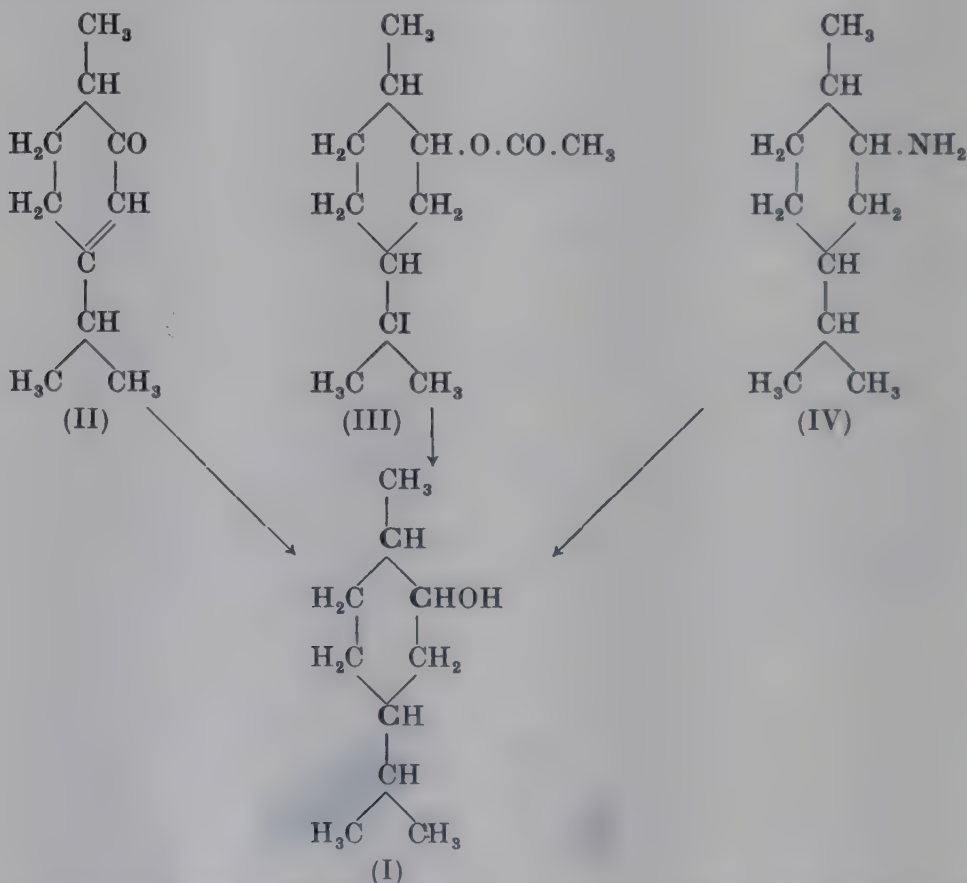
¶ *Ber.* 1910, **43**, 2525; 1912, **45**, 463; 1917, **50**, 713; 1920, **53**, 2385.

CARVOMENTHOL (TETRAHYDROCARVEOL)

(p-Menthan-2-ol or 1-Methyl-4-isopropylcyclohexan-2-ol)



Carvomenthol (I), which does not appear to occur in nature, was prepared practically simultaneously by Wallach* by the reduction of *carvenone* (II) and by Baeyer† by the reduction of the acetyl derivative of *dihydrocarveol hydroiodide* (III), followed by hydrolysis of the acetate so obtained.



* *Annalen*, 1893, 277, 130.

† *Ber.* 1893, 26, 822.

Since carvomenthol contains three asymmetric carbon atoms, shown in clarendon type in (I), it can exist in eight optically active and four externally compensated modifications. Active and racemic forms of the alcohol have been described, but only recently have attempts been made to prepare the optically pure isomerides. When obtained by any of the methods referred to, the product is always a mixture of stereoisomerides.

In addition to its formation by the reduction of carvone, carvenone, carvotanacetone and carvomenthone (see pp. 329, 341, 347, 396) it can also be obtained by the reduction of nitro- α -phellandrene,* by the action of nitrous acid on carvomenthylamine (IV),† and by the hydrogenation of carvacrol, in the presence of nickel, at 160°.‡ Other methods developed by Read for the isolation of particular stereoisomers, are discussed below.

Carvomenthol is a colourless, somewhat viscid oil, with an odour resembling terpeneol. The mixture of stereoisomers-usually obtained has b.p. 220°, d^{22}_D 0.904, n^{22}_D 1.4636.§ It can be identified by the preparation of the *phenylurethane*, m.p. 74–75°, or the *allophanate*,|| m.p. 192.5°, though it is unlikely that these derivatives are stereochemical individuals.

Paolini¶ attempted to isolate a number of the stereoisomeric carvomenthols in a state of purity by fractional crystallisation of the hydrogen phthalates and resolution of these esters by the use of strychnine. A consideration of the physical properties of the products suggested that five of the alcohols had been obtained pure, but it appears from the later work of Read and Johnston** that these results were fortuitous, and that the products were in fact mixtures. Read and Johnston approached the problem by studying each stage in the reduction of *carvone* (V) through *dihydrocarvone* (VI), *carveol* (VII), and *dihydrocarveol* (VIII), to *carvomenthol* (I). It will be seen that by this procedure, the number of asymmetric carbon atoms (shown in clarendon type)

* Wallach and Herbig, *Annalen*, 1895, **287**, 377; Wallach and Beschke, *ibid.* 1904, **336**, 32.

† Wallach, *ibid.* 1895, **287**, 380.

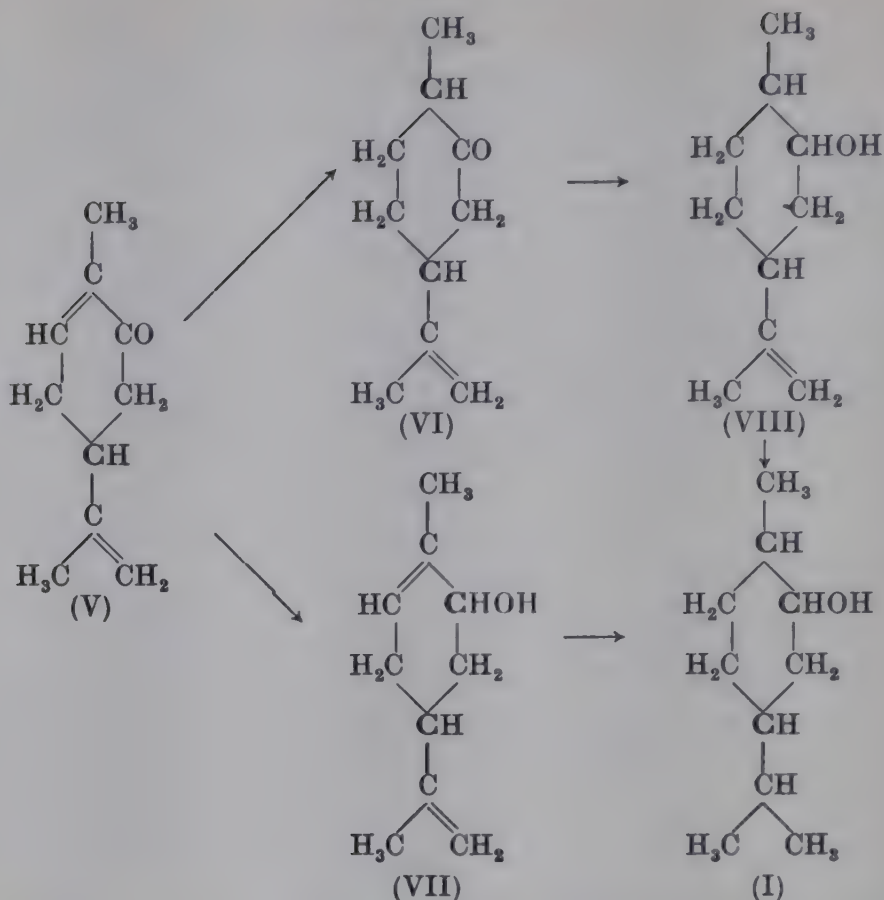
‡ Brunel, *Compt. rend.* 1903, **137**, 1269; 1905, **141**, 1246; compare Henderson and Schotz, *J.C.S.* 1912, **101**, 2565.

§ Wallach, *Annalen*, 1893, **277**, 130.

|| Béhal, *Bull. Soc. chim.* 1919 [iv], **25**, 479.

¶ *Atti R. Accad. Lincei*, 1919 [v], **28**, II, 82, 134; *Gazzetta*, 1925, **55**, 818.

** *J.C.S.* 1934, pp. 226, 233; 1935, p. 1138.



is increased one at a time, and it is therefore a comparatively straightforward matter to separate the products at any one stage, provided that the precursor itself has been rigorously purified. The methods adopted for these separations have been based largely on previous experience in the menthol field (see p. 239); some of the stereoisomers have also been prepared from the corresponding carvomenthylamines.* As a result of this work, one optically active form of each carvomenthol has been obtained, and their properties, together with those of some derivatives, are given in the table:

	B.p.	d_{4}^{20}	n_D^{20}	$[\alpha]_D^{16}$	M.p. of derivatives	
					p-Nitro-benzoate	3:5-Dinitro-benzoate
<i>d</i> -Carvomenthol	102°/14 mm.	0.8995	1.4617	+26°	60°	107°
<i>l-neo</i> Carvomenthol	96°/11 mm.	0.9012	1.4644	-42°	95°	129°
<i>l-iso</i> Carvomenthol	106°/17 mm.	0.9109	1.4662	-18°	64.5°	111°
<i>l-neoiso</i> Carvomenthol	—	0.9102	1.4676	-35°	54-55°	71-72°

Our knowledge of the carvomenthylamines is not equally complete, for *neoisocarvomenthylamine* has not yet been

* Compare Dodge and Kremers, *J. Amer. Pharm. Assoc.* 1942, **31**, 525.

prepared. The physical properties of the known isomers are summarised below:

	B.p.	d_4^{25}	n_D^{25}	$[\alpha]_D^{25}$	M.p. of derivatives		
					Formyl-	Acetyl-	Benzoyl-
<i>d</i> -Carvomenthylamine	90°/16 mm.	0.8505	1.4578	+13°	95°	161°	161°
<i>l-neo</i> Carvomenthylamine	88°/16 mm.	0.8558	1.4596	-27°	50°	114°	126°
<i>l-iso</i> Carvomenthylamine	90°/15 mm.	0.8587	1.4611	-14°	—	96°	153°

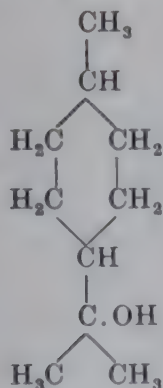
The configurations of the carvomenthols and the carvomenthylamines have not yet been finally established. It is known, however, that the *d*- and *l-neo*carvomenthols are related to *l*-carvomenthone, whilst the *l-iso*- and *l-neoisoc*arvomenthols are related to *l-isoc*arvomenthone.

Carvomenthol shows the usual properties of saturated secondary alcohols. It can be oxidised readily to the corresponding ketone, and a number of esters have been prepared. According to Brunel,* when the alcohol is passed with hydrogen over nickel at 230–240° it is dehydrogenated to carvacrol, whilst, when heated with potassium hydrogen sulphate† or boric anhydride,‡ it yields Δ^1 -*p*-menthene. By treatment with hydrogen chloride or bromide 2-*chloro*- (or *bromo*-)*p*-menthane is formed which on digestion with alkali gives Δ^1 -*p*-menthene.§

Halogen derivatives of the alcohol have been prepared from dihydrocarveol but they are somewhat unstable.

DIHYDRO- α -TERPINEOL

(*p*-Menthan-8-ol or 1-Methyl-4-isopropylcyclohexan-8-ol)



* *Compt. rend.* 1910, **150**, 1529.

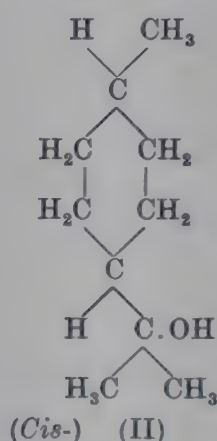
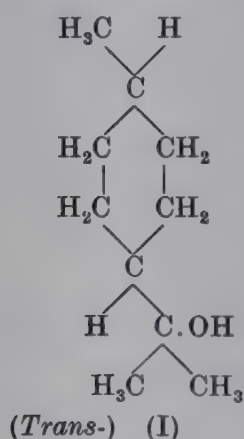
† Wallach, *Annalen*, 1893, **277**, 130.

‡ Mereshkovski, *J. Russ. Phys. Chem. Soc.* 1913, **45**, 1686.

§ Kondakov and Lutschinin, *J. pr. Chem.* 1899 [ii], **60**, 273.

The *trans*-modification of dihydro- α -terpineol has been found by Zeitschel and Schmidt* to be present in the so-called American wood turpentine, "Pine-oil". Wallach† had observed that when α -terpineol was reduced with hydrogen in the presence of a palladium catalyst, it gave a saturated alcohol, the *phenylurethane* of which melted at 117–118°, whilst Béhal,‡ making use of the Sabatier-Senderens method with a nickel catalyst, had obtained an isomeric alcohol yielding a *phenylurethane*, m.p. 94–95°.

The nature of the relationship of these two alcohols was not determined at the time, but Zeitschel and Schmidt have shown them to be *cis-trans*-isomerides, which may be represented by the formulae (I) and (II).



Trans-dihydro- α -terpineol, from "Pine-oil", crystallises from light petroleum in hard needles, m.p. 34.6–35.2°, b.p. 209.3–209.5°/760 mm., d_{20}^{20} 0.901, n_D^{20} 1.4630, and yields a *phenylurethane*, m.p. 117–118°. It is identical in all respects with the alcohol described by Wallach. When α -terpineol was reduced by Béhal's method, Zeitschel and Schmidt found that the resulting saturated alcohol was a mixture, yielding a small amount of the more sparingly soluble phenylurethane, m.p. 117–118°, derived from the *trans*-alcohol, whilst, from the mother liquor, the phenylurethane of the *cis*-alcohol, m.p. 94–95°, was separated. By the hydrolysis of this the pure *cis*-alcohol was prepared. This was an oil and did not crystallise when cooled: b.p. 210–

* *Ber.* 1927, **60**, 1372.

† *Annalen*, 1911, **381**, 55.

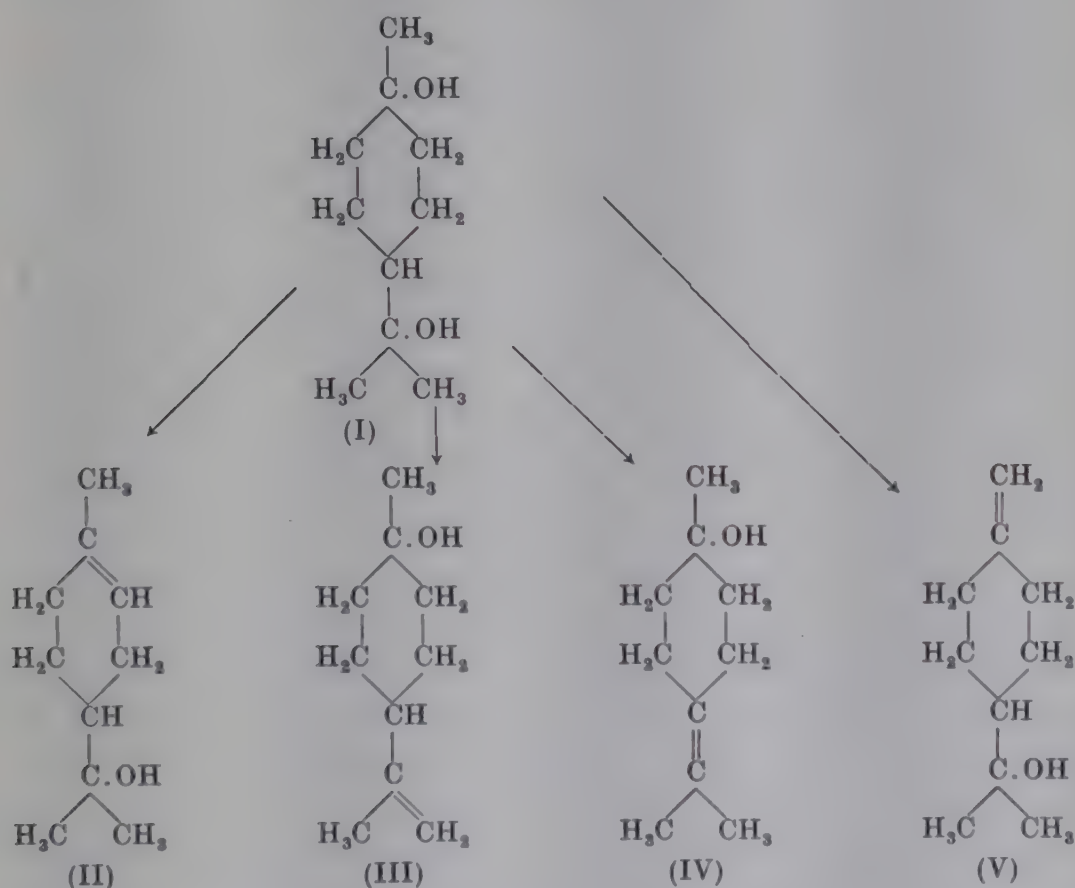
‡ *Compt. rend.* 1910, **150**, 1762.

210.5°/760 mm., d_{20}^{20} 0.9124, n_D^{20} 1.4655. It will be observed that in accordance with the general rule,* the *cis*-form of the alcohol has a somewhat higher density and refractive index than the *trans*-.

THE TERPINEOLS

The name *terpinol* or *terpineol* was applied originally to the mixture of alcohols formed when the glycol, *terpin*, was treated with dehydrating agents.

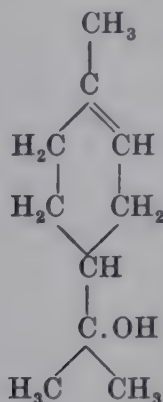
On dehydration terpin (I) can theoretically give rise to four isomeric unsaturated alcohols, $C_{10}H_{18}O$, represented by formulae (II), (III), (IV) and (V). With the exception of the alcohol (V) all these are known and have been designated at Wallach's suggestion α -, β - and γ -terpineols.



* Auwers, *Annalen*, 1915, 410, 287; 1920, 420, 91.

α -TERPINEOL

(Δ^1 -p-Menthen-8-ol or 1-Methyl-4-isopropyl- Δ^1 -cyclohexen-8-ol)



α -Terpineol occurs in nature both in the optically active and inactive modifications in the free state and in the form of its esters. These are somewhat widely distributed,* the *d*-form having been separated *inter alia* from the oils of petitgrain and neroli, the *l*- from camphor oils and the *dl*- from cajuput oil.

Although the removal of one molecule of water from terpin (p. 300) with formation of an alcohol was reported by Wiggers[†] and by List,[‡] the products examined by these investigators were clearly very impure and the pure alcohol would appear to have been first prepared by Tilden.[§] Tilden, who dehydrated terpin with dilute sulphuric acid, gives the boiling-point of the alcohol as 205–215°; he correctly determined the empirical formula, $C_{10}H_{18}O$, and he showed that on treatment with hydrogen chloride, it gave a dichloride (dipentene dihydrochloride), m.p. 48°, from which, by the action of water, the alcohol could be regenerated. He also succeeded in hydrating the alcohol with re-formation of terpin. At approximately the same time Flavitzky^{||} prepared, by the action of alcoholic sulphuric acid on dextro- and laevo-rotatory oils of turpentine (pinene), two optically active alcohols of the same composition.

Although it was recognised by 1880 that terpineol was an alcohol of the formula $C_{10}H_{17}OH$, which could be prepared by

* Gildemeister and Hoffmann, *Die Ätherischen Öle*, 3rd ed., vol. I, 453.

† *Annalen*, 1846, 57, 252.

‡ *Ibid.* 1848, 67, 367.

§ *J.C.S.* 1878, 33, 247; 1879, 35, 287; *Ber.* 1879, 12, 848, 1131.

|| *Ber.* 1879, 12, 857, 1022, 2354.

the dehydration of the glycol, *terpin*, $C_{10}H_{20}O_2$, yet there was still considerable confusion as to the relationship of these two substances and the conditions governing their interconversion. Much of this obscurity was dispelled by the publication in 1885 by Wallach* of two papers on the action of various dehydrating agents on *terpin* and on the relationship of the products formed in the reaction. He showed that with very weak dehydrating agents the main product was an unsaturated alcohol, *terpineol*,† $C_{10}H_{17}OH$. He confirmed Tilden's observation of the formation of a crystalline dichloride and he pointed out that whereas the introduction of one of the halogen atoms was due to the addition of hydrogen chloride to an ethylenic linkage, the other was due to the replacement of a hydroxyl group. Wallach also prepared from the alcohol a crystalline *phenylurethane*.

In the following year Bouchardat and Lafont‡ made the very important observation that *terpineol* could be obtained crystalline. By heating dipentene with acetic acid at 100° for 60 hours they obtained an acetyl derivative from which on hydrolysis an alcohol was prepared, which crystallised when cooled to -50° . This crystalline alcohol, m.p. $30-32^\circ$, was prepared subsequently by Bouchardat and Voiry§ by the dehydration of *terpin*. With the introduction of the commercial manufacture of a crystalline *terpineol*, m.p. 35° , shown by Wallach|| to be identical with that previously investigated by him, the further work on this alcohol was much facilitated.

Constitutional formulae for *terpin* (I) and *terpineol* (II) were first suggested by Brühl,¶ and these received general acceptance, although certain facts were known which were not quite consonant therewith. It was difficult to account for the oxidation of α -*terpineol* to *terpenylic acid*, the constitution of which had been determined by Schryver,** and an even greater objection was that on dehydration it could only give rise to a hydrocarbon containing no asymmetric carbon atom, whereas actually the

* *Annalen*, 1885, 227, 286; 230, 247.

† This name was introduced by Wallach and was subsequently modified by him to α -*terpineol* with the discovery of the isomeric alcohols, β - and γ -*terpineols*, in commercial *terpineol*.

‡ *Compt. rend.* 1886, 102, 1555.

§ *Ibid.* 1887, 104, 996; *Bull. Soc. chim.* 1887 [ii], 47, 870; it is not quite certain whether these authors actually obtained α - or β -*terpineol* since both would be present in the mixtures examined by them.

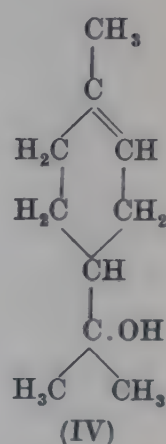
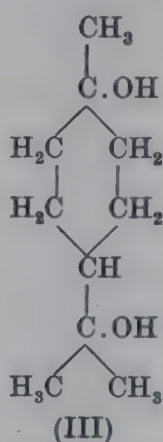
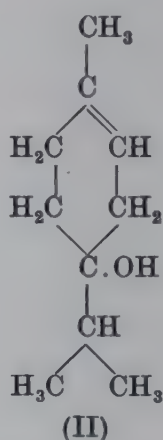
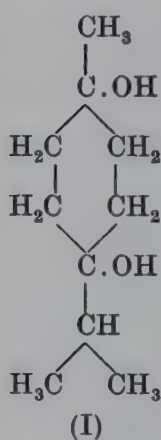
|| *Annalen*, 1893, 275, 104.

¶ *Ber.* 1888, 21, 464.

** *J.C.S.* 1893, 63, 1338.

d- and *l*-forms of the alcohol could be prepared from *d*- and *l*-limonenes. To overcome this latter difficulty Baeyer suggested that the optical activity of the limonenes was due, not to an asymmetric carbon atom, but to the asymmetry of the molecule as a whole.

In 1894 Wagner,* on the basis of his new formula for α -pinene, suggested that terpin and α -terpineol were more correctly represented by (III) and (IV). These formulae were advanced on purely theoretical grounds and were not supported by any fresh direct experimental evidence, but their correctness was very soon recognised, the more especially since the formation of terpenylic acid and other degradation products of α -terpineol was readily accounted for.



The first systematic experiments on the oxidation of *dl*- α -terpineol were made by Wallach,[†] who showed that on oxidation with dilute potassium permanganate, a *glycerol*, $\text{C}_{10}\text{H}_{20}\text{O}_3$, m.p. $121\text{--}122^\circ$, was obtained in an almost quantitative yield. On dehydration the glycerol gave a mixture of *p*-cymene and the ketone, carvenone, whilst on oxidation with chromic acid a substance, $\text{C}_{10}\text{H}_{16}\text{O}_3$, m.p. $62\text{--}63^\circ$, was obtained; the latter, by further degradation, gave terpenylic acid. The constitution of the substance, $\text{C}_{10}\text{H}_{16}\text{O}_3$, was not at the time determined, but some years later, after the adoption of Wagner's formula for the alcohol, Wallach[‡] and Tiemann and Semmler[§] simultaneously advanced a correct interpretation of the mechanism of the degradation of α -terpineol.

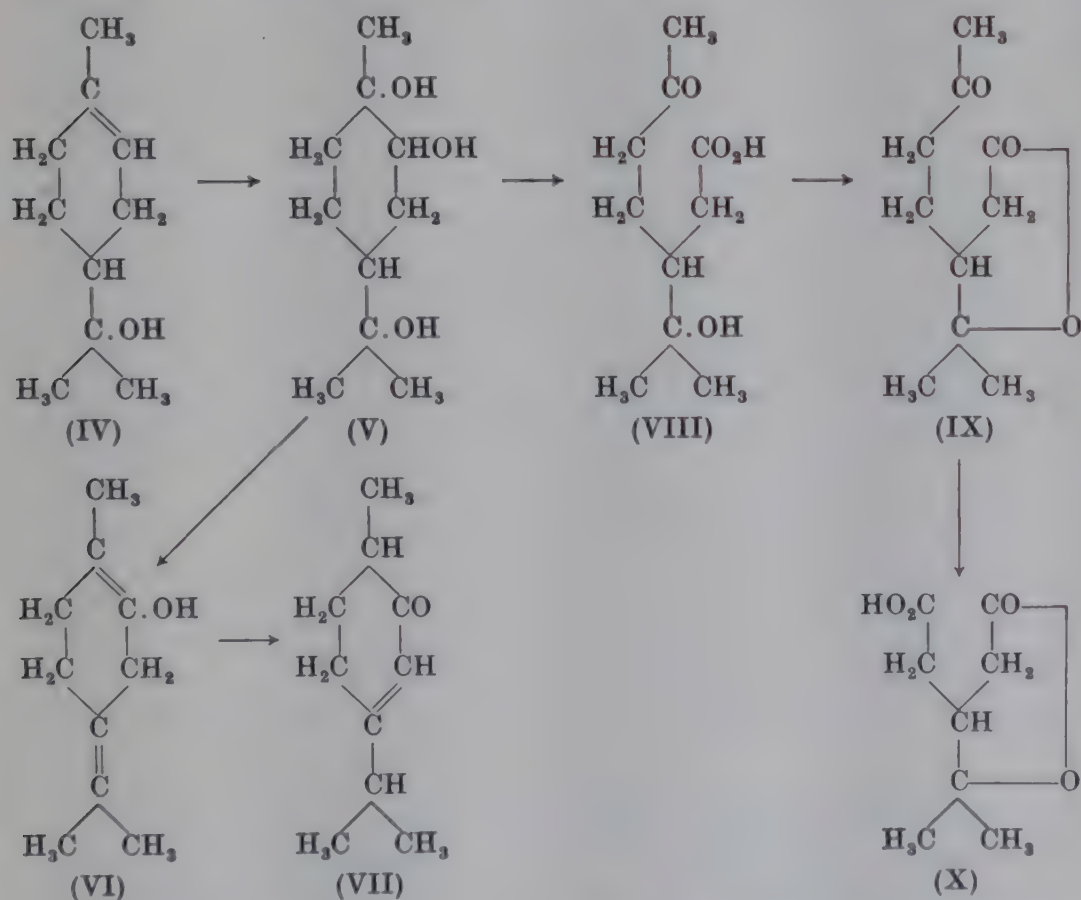
* *Ber.* 1894, 27, 1652.

‡ *Ber.* 1895, 28, 1775.

† *Annalen*, 1893, 275, 151; 277, 110.

§ *Ibid.* p. 1778.

The primary product of the reaction, the glycerol, was shown to be *p*-menthane-1:2:8-triol (V), the ethylenic linkage having reacted in accordance with the Wagner rule. From this on dehydration *p*-cymene and *carvenone* (VII) were formed, the latter probably by the intermediate stage of (VI). The substance $C_{10}H_{16}O_3$ was shown to be a ketonic lactone, *homoterpenyl methyl ketone* (IX), formed by loss of water from the γ -hydroxy-acid (VIII). This ketone was characterised by the preparation of the *oxime*, m.p. $80-81^\circ$, and the *semicarbazone*, m.p. 200° , whilst the presence of the lactone ring was established by titration with an excess of alkali. The optically active lactonic ketone, m.p. $48-49^\circ$, was first identified by Baeyer and Baumgartel,* although it had been prepared previously by Godlewski† by the degradation of *l*- α -terpineol. The formation of *terpenylic acid* (X) by oxidation of the lactone with potassium permanganate was also readily explained. It may be noted that, contrary to anticipation, homoterpenyl methyl ketone cannot be oxidised with



* Ber. 1898, 31, 3217.

† J. Russ. Phys. Chem. Soc. 1896, 28, 140.

sodium hypobromite to homoterpenylic acid, but undergoes some profound, and at present undetermined, change. The structure of this ketone has been confirmed by synthesis.*

The determination of the constitution of the degradation products left no doubt that the formula suggested by Wagner correctly represented the structure of α -terpineol, and this was fully confirmed by the rational synthesis of the alcohol by W. H. Perkin, jun.,† which is described on p. 150.

The constants, more especially the rotatory powers, of the α -terpineols from natural sources, as quoted in the literature, show somewhat wide variations. For a dextrorotatory alcohol derived from oil of sweet oranges Stephan‡ gives m.p. 38–40°, b.p. 219–221°/760 mm., d^{15}_D 0.938, n^{18}_D 1.4832, $[\alpha]_D + 95.9^\circ$. This alcohol must have been optically pure since Fuller and Kenyon,§ who prepared the alcohol by the hydrolysis of *d*- α -terpenyl hydrogen phthalate, which had been obtained by the resolution of the *dl*-ester with brucine, found m.p. 36.9°, b.p. 104°/15 mm., d^{14}_D 0.9475, n_D 1.4819, $[\alpha]^{20}_D \pm 100.5^\circ$, whilst Paolini,|| who used strychnine for the resolution of the phthalate, gives the rotatory power as $+98.5^\circ$. A much higher value, $[\alpha]_D - 117.5^\circ$, has been recorded by Ertischikowski,¶ but this is undoubtedly too high. *dl*- α -Terpineol melts at 35°, b.p. 218.8–219.4°/752 mm., d^{20}_{20} 0.935, n^{20}_D 1.4831, and values closely agreeing with these were observed by Kay and Perkin, jun.** for the synthetic alcohol.

α -Terpineol forms a number of crystalline derivatives, so that its identification is easy. Most convenient for this purpose are the *phenylurethane*, *d*- and *l*-forms, m.p. 109.5°, *dl*-, m.p. 113°, and the *nitrolpiperidides*, prepared from the crystalline *nitrosochlorides*, *d*- and *l*-, m.p. 151–152°, *dl*-, m.p. 159–160°. The *allophanate*, m.p. 133–134°, has been described by Naves and Grampoloff.††

α -Terpineol can be prepared most conveniently by the dehydration of terpin, for which a great variety of reagents may be employed. In view of the technical importance of the alcohol,

* Owen and Simonsen, *J.C.S.* 1932, p. 1424.

† *J.C.S.* 1904, 85, 416; Fisher and Perkin, jun., *ibid.* 1908, 93, 1871.

‡ *J. pr. Chem.* 1900 [ii], 62, 530.

§ *J.C.S.* 1924, 125, 2304.

|| *Gazzetta*, 1925, 55, 804.

¶ *J. Russ. Phys. Chem. Soc.* 1896, 28, 136; *Bull. Soc. chim.* 1896 [iii], 16, 1585.

** *J.C.S.* 1906, 89, 851.

†† *Helv. Chim. Acta*, 1942, 25, 1500.

which finds an extended application in the perfumery industry, this reaction has been closely studied. The manufacture from terpin was commenced about 1888, as the outcome of the researches of Wallach referred to above, phosphoric acid being used as the dehydrating agent. Since that date numerous modifications in the process have been introduced, for details of which reference must be made to the patent literature. In addition to its manufacture from terpin, α -terpineol can be prepared directly from oil of turpentine (pinene) by the action of sulphuric acid in acetic acid or alcoholic solution, when the optically active modifications of the alcohol are obtained of the same sign as the original hydrocarbon.* Many modifications of this process are described in the technical literature.

When terpineol is prepared by any of these processes a mixture of isomeric alcohols is obtained. This mixture was shown by Stephan and Helle† to be separable by fractional distillation into α - and β -terpineols (compare p. 267); subsequently Wallach and Meister‡ showed terpinen-1-ol also to be present (see p. 279), whilst the investigations of Baeyer (p. 272) indicate the probable occurrence also of γ -terpineol.

In addition to the processes mentioned, *d*-, *l*- and *dl*- α -terpineols have been prepared by a number of other reactions. The alcohol can be obtained by the action of oxides of nitrogen on pinene;§ by the cyclisation of linalool and geraniol with either acetic anhydride, formic acid or a mixture of sulphuric and acetic acids.|| It is formed also by the hydration of dipentene or by the action of dilute alkali on dipentene dihydrochloride, or from terpinene dihydrochloride by treatment with silver acetate followed by hydrolysis of the terpinyl acetate so obtained.¶ Its presence was observed amongst the products formed by the oxidation of α -pinene with hydrogen peroxide,** and Pickard and Kenyon†† obtained it by heating to 170° the additive compound which cineole gives when treated with methyl magnesium iodide.

* Flavitzky, *Ber.* 1887, **20**, 1957; Bertram, *G.P.* 67255.

† *Ber.* 1902, **35**, 2148.

‡ *Annalen*, 1908, **362**, 269.

§ Genvresse, *Compt. rend.* 1901, **132**, 639.

|| Stephan, *J. pr. Chem.* 1898 [ii], **58**, 111; 1899 [ii], **60**, 244; Bertram, *G.P.* 80711

¶ Wallach, *Annalen*, 1906, **350**, 154.

** Henderson and Sutherland, *J.C.S.* 1912, **101**, 2288.

†† *Ibid.* 1907, **91**, 904.

Cineole can also be converted into α -terpineol by digestion with acetic anhydride.*

The catalytic hydrogenation of α -terpineol by the Sabatier-Senderens process with a nickel catalyst gives, according to the experimental conditions used, either dihydroterpineol[†] (see p. 254), *p*-menthane[‡] or *p*-cymene.[§] With a copper catalyst dipentene is said by Neave^{||} to be the main product. Dihydroterpineol can be prepared also by hydrogenation in the presence of colloidal palladium.[¶]

The oxidation of α -terpineol with ozone has been found by Harries^{**} to give the normal ozonide, $C_{10}H_{17}OH(O_3)$, but with nitric acid there is very complete degradation with formation of *terpenylic* and *terebic acids*, the former acid, together with homoterpenyl methyl ketone, being obtained with chromic acid.^{††} With Caro's reagent, Baeyer and Villiger^{**} obtained the same glycerol as is formed by the action of potassium permanganate. The autoxidation of α -terpineol has been studied by Dupont.^{§§}

With bromine α -terpineol gives in acetic acid solution a liquid *dibromide* (XI),^{|||} which was found by Baeyer to react with hydrogen bromide to give a tribromide, 1:2:8-*tribromo-p-menthane* (XII).

This bromide was also an oil and it is interesting to note that on further bromination it gives *dipentene tetrabromide* (XIII), a reaction which implies either elimination of hydrogen bromide followed by addition of bromine to the ethylenic linkage so formed, or else direct bromination of the methyl group, which would appear improbable.

The dibromide is not stable, and on warming is converted into *p*-cymene,^{¶¶} an example of the method introduced by Baeyer and Villiger for the dehydrogenation of cyclic bodies by exhaustive bromination.

* Knoevenagel, *Annalen*, 1914, **402**, 141.

† Béhal, *Compt. rend.* 1910, **150**, 1763.

‡ Haller and Martine, *Compt. rend.* 1905, **140**, 1298.

§ Sabatier and Gaudion, *Compt. rend.* 1918, **168**, 671.

|| *J.C.S.* 1912, **101**, 514.

¶ Wallach, *Annalen*, 1911, **381**, 55.

** *Ber.* 1912, **45**, 942; compare Briner, Mottier and Paillard, *Helv. Chim. Acta*, 1930, **13**, 1030.

†† Tiemann and Schmidt, *Ber.* 1895, **28**, 1783.

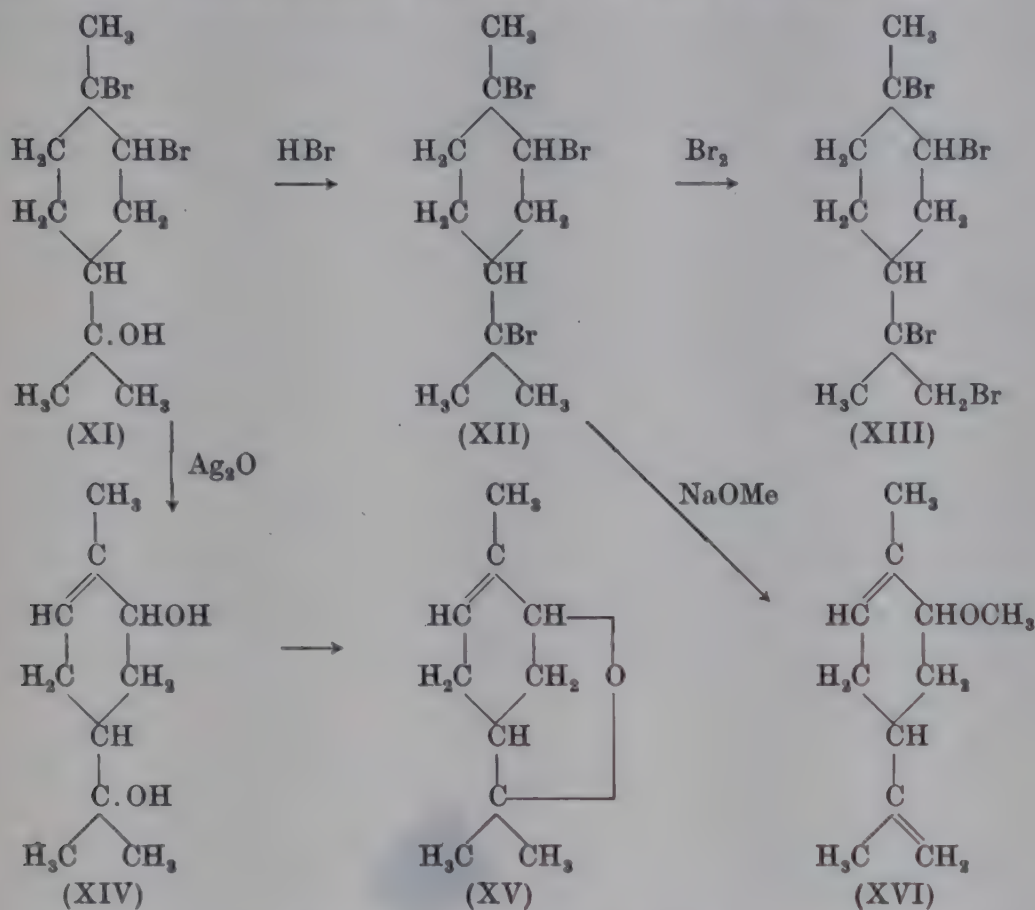
** *Ibid.* 1899, **32**, 3633.

§§ *Ind. chim. belge*, 1940 [2], **11**, 3.

||| Wallach, *Annalen*, 1893, **277**, 113.

¶¶ Wallach, *ibid.* 1918, **414**, 206.

When the dibromide was treated with silver oxide, it was found by Wallach* to give a mixture of *pinol hydrate* (XIV) and *pinol* (XV), whilst, from the tribromide by the action of sodium methoxide, *carveol methyl ether* (XVI) was prepared.†



With sodium hypochlorite α -terpineol gives two isomeric *chlorohydrins*, m.p. 114–115° and 60–80°,‡ which are probably *cis-trans*-isomerides. With the halogen acids, the alcohol yields the corresponding dipentene dihalogenides.

The elimination of water from α -terpineol takes place with great ease and in all cases a mixture of hydrocarbons is produced. With potassium bisulphate or active carbon the main product is dipentene, whilst formic acid and aqueous oxalic acid are stated to give chiefly terpinolene; in every case, however, terpinene is also formed in not inconsiderable quantity.§ The

* *Annalen*, 1893, **277**, 113; compare Slawinski and Hofszajn, *Schimmel's Report*, 1931, p. 170.

† *Annalen*, 1894, **281**, 141.

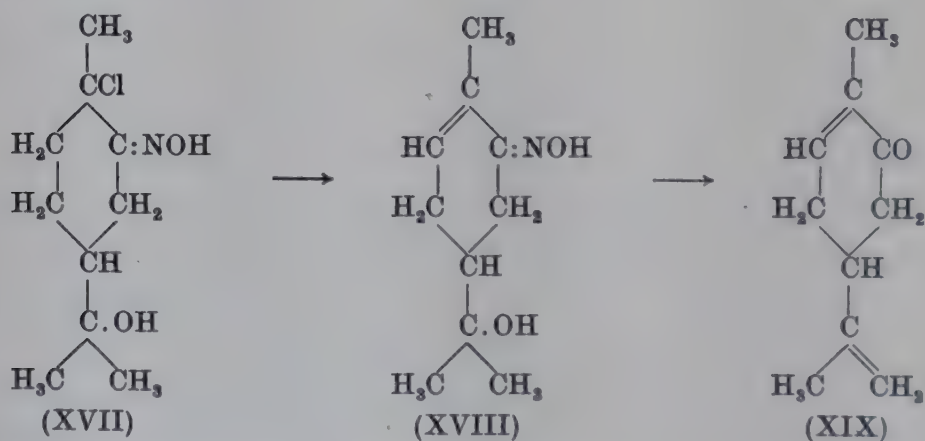
‡ Slawinski, *Chemik Polski*, 1917, **15**, 97.

§ Wallach, 1885, **230**, 225; 1893, **275**, 104; 1896, **291**, 361; Baeyer, *Ber.* 1894, **27**, 447; Kimura, *Bull. Chem. Soc. Japan*, 1935, **10**, 330; Alder and Rickert, *Ber.* 1937, **70**, 1364; Ipatiev and Pines, *J. Amer. C.S.* 1944, **66**, 1120.

dehydration of α -terpineol to dipentene with comparatively little isomerisation can apparently be effected conveniently with methyl magnesium iodide, but even this reagent causes almost complete racemisation.* Fuller and Kenyon† have, however, found that when either *d*- or *l*- α -terpenyl hydrogen phthalates are hydrolysed with alkali, considerable conversion into *d*- and *l*-limonenes occurs with practically no racemisation.

As was first observed by Tilden,‡ when α -terpineol is allowed to remain in contact with dilute mineral acids it is hydrated with formation of terpin; Aschan§ has shown that the change is almost quantitative with sulphuric acid (40 per cent.) at 0°.

α -Terpineol nitrosochloride (XVII), which is bimolecular, was prepared by Wallach.|| The *d*- and *l*-forms melt at 107–108° and the *dl*- at 120–122°; more convenient for identification are, however, the nitrolpiperidides (compare p. 260). When the nitrosochlorides are treated with sodium methoxide, 8-hydroxycarvotanacetoxime (XVIII), m.p. 133–134°, is obtained, which is converted by the action of dehydrating agents into *carvone* (XIX) or by the action of concentrated mineral acids into aminothymol.¶



The *semicarbazone* of 8-hydroxycarvotanacetone is obtained when the nitrosochloride is heated with semicarbazide hydrochloride, α -terpineol being also formed. The reaction proceeds obviously with the prior formation of the ketone, which then reacts with the excess of semicarbazide. Of interest also is the

* Fisher and Perkin, jun., *J.C.S.* 1908, **93**, 1875.

† *Ibid.* 1924, **125**, 2304.

‡ *Ibid.* 1879, **35**, 289.

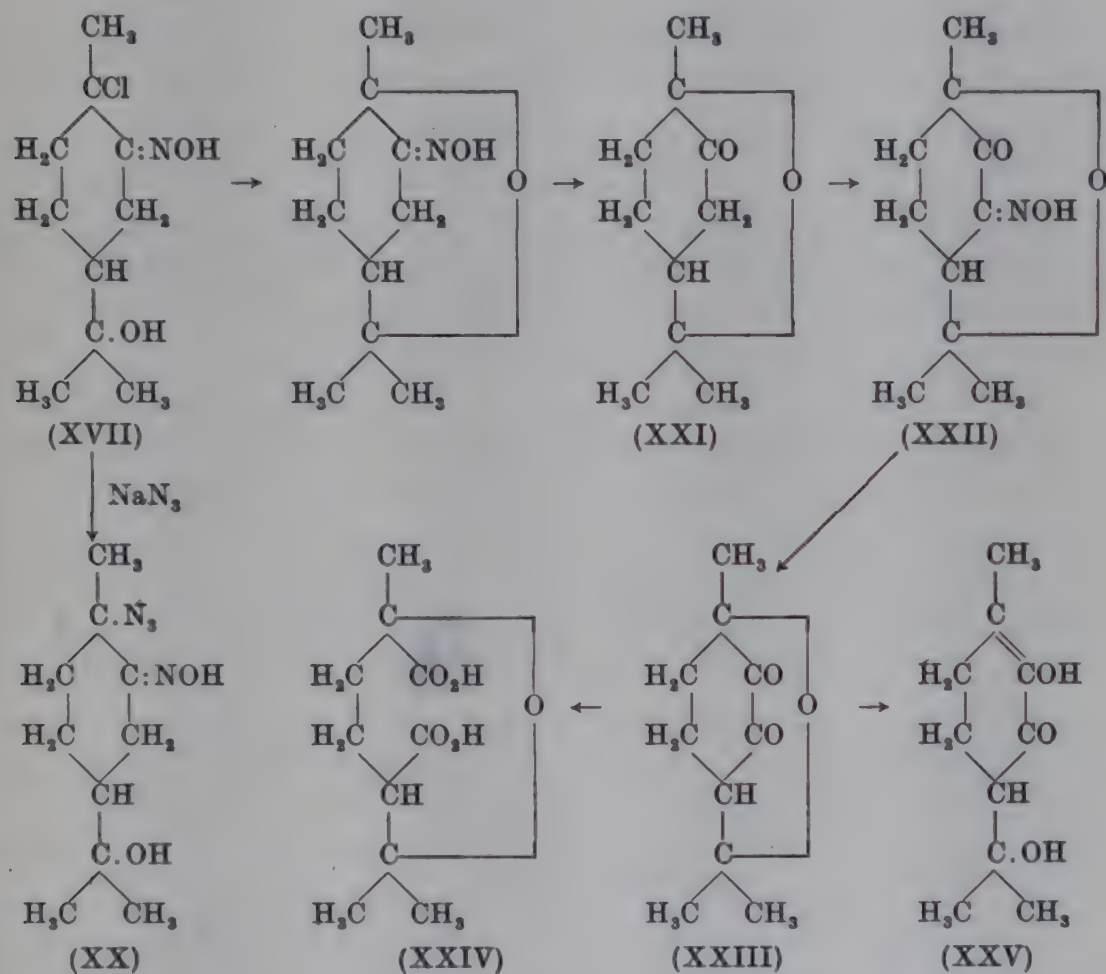
§ *Bidrag til Kännedom af Finland*, 1918, **77**, 1.

|| *Annalen*, 1893, **277**, 120.

¶ Wallach, *ibid.* 1906, **345**, 128.

interaction of the nitrosochloride with sodium azide, yielding α -terpineol nitrosoazide (XX), m.p. 111° , from which by the action of alkali the hydroxy-ketone can be prepared.*

Cusmano[†] has found that by the action of alcohol on the nitrosochloride, *keto-cineole* (XXI) (*d*-, m.p. 50° ; *dl*-, m.p. 42°) is produced. The reactions of this substance have been studied in some detail and of particular interest is its conversion through its isonitroso-derivative (XXII), m.p. 132° , into the



yellow *diketo-cineole* (XXIII). This gives *cineolic acid* (XXIV) on oxidation and on reduction *hydroxydiosphenol* (XXV). The conversion of *keto-cineole* into *diosphenol* is referred to on p. 418. Reduction of *keto-cineole* gives two isomeric *hydroxycineoles*, m.p. 80° and 108° .[‡]

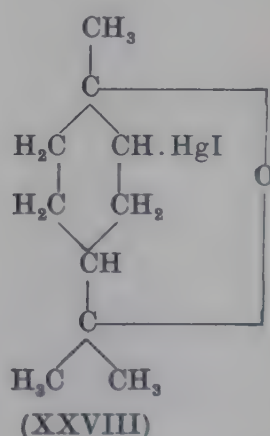
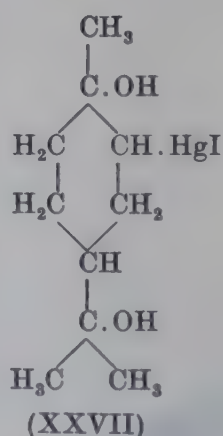
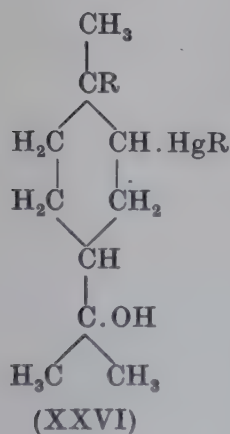
* Forster and Newman, *J.C.S.* 1911, **99**, 250.

† *Gazzetta*, 1919, **49**, i, 26; 1923, **53**, i, 195; 1925, **55**, 140; 1942, **72**, 68.

‡ Ishidate, *J. pharm. Soc. Japan*, 1928, **48**, 9; Gandini, *Gazzetta*, 1937, **67**, 113.

In addition to those separated from essential oils, a large number of esters of α -terpineol has been prepared, since they are of technical importance. These do not require special mention, but attention must be directed to the fact that the usual methods of esterification do not give good yields, owing to the tendency for dehydration to occur with formation of dipentene and other hydrocarbons. The *formate* and *acetate* are conveniently prepared by the action of formic acid and acetic anhydride respectively on either pinene or geraniol.* Direct preparation of the esters from the alcohol can be effected in excellent yield from the potassium salt. In this manner Fuller and Kenyon[†] prepared *dl- α -terpenyl hydrogen phthalate*, m.p. 117–118°, which could be readily resolved by strychnine into its optical enantiomorphs. These authors also prepared and studied the rotatory powers of a number of optically pure esters. The *methyl ether* of α -terpineol has been prepared by Treibs[‡] by the action of methyl alcohol and sulphuric acid on α - and β -pinenes.

Mercury derivatives of α -terpineol have been obtained by Sand and Singer[§] by the action of mercury salts on the alcohol in alkaline solution. These compounds have the general formula (XXVI) ($R = \text{Cl, Br or I}$) and, when treated with an aqueous solution of potassium iodide, give a mixture of *trans-terpin mercuri-iodide* (XXVII) and the *mercuri-iodide* derivative of cineole (XXVIII).



* Lafont, *Bull. Soc. chim.* 1888 [ii], **49**, 325; Lafont and Bouchardat, *Ann. chim.* 1889 [vi], **16**, 244; Stephan, *J. pr. Chem.* 1899 [ii], **60**, 244; compare Paillard and Tempia, *Helv. Chim. Acta*, 1931, **14**, 1314.

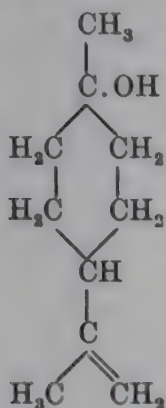
[†] *J.C.S.* 1924, **125**, 2304.

[‡] *Ber.* 1937, **70**, 593.

[§] *Ibid.* 1902, **35**, 3170; *Annalen*, 1903, **329**, 141.

β -TERPINEOL

($\Delta^{8(9)}$ -p-Menthen-1-ol or 1-Methyl-4-isopropenylcyclohexan-1-ol)



β -Terpineol, $C_{10}H_{18}O$, has not been found to occur in nature. It was first separated in a pure state from the lower boiling fraction of commercial "terpineol" by Stephan and Helle,* although it is not improbable that the alcohol, m.p. $30-32^\circ$, which Bouchardat and Voiry† prepared by the action of dilute sulphuric acid on terpin hydrate, was identical with β -terpineol.

By prolonged fractional distillation of "terpineol" Stephan and Helle succeeded in separating two fractions: (i) b.p. $212-215^\circ$, d^{15}_4 0.930, and (ii) b.p. $218-220^\circ$, d^{15}_4 0.940. The higher boiling fraction consisted essentially of α -terpineol, m.p. 35° , whilst the lower boiling fraction on cooling deposited β -terpineol, m.p. $32-33^\circ$.

The constitution of the alcohol was shown to be represented by (I) by an investigation of the products formed on oxidation with dilute potassium permanganate.‡ The primary product is the crystalline glycerol, p-menthane-1:8:9-triol (II), m.p. $118-118.5^\circ$, which, on further oxidation with chromic acid, gives the hydroxy-ketone (III) (b.p. $140-145^\circ/19$ mm., semicarbazone, m.p. $195-196^\circ$) together with the unsaturated ketone (IV) (b.p. $68.5-70^\circ/4$ mm., semicarbazone, m.p. 160°).

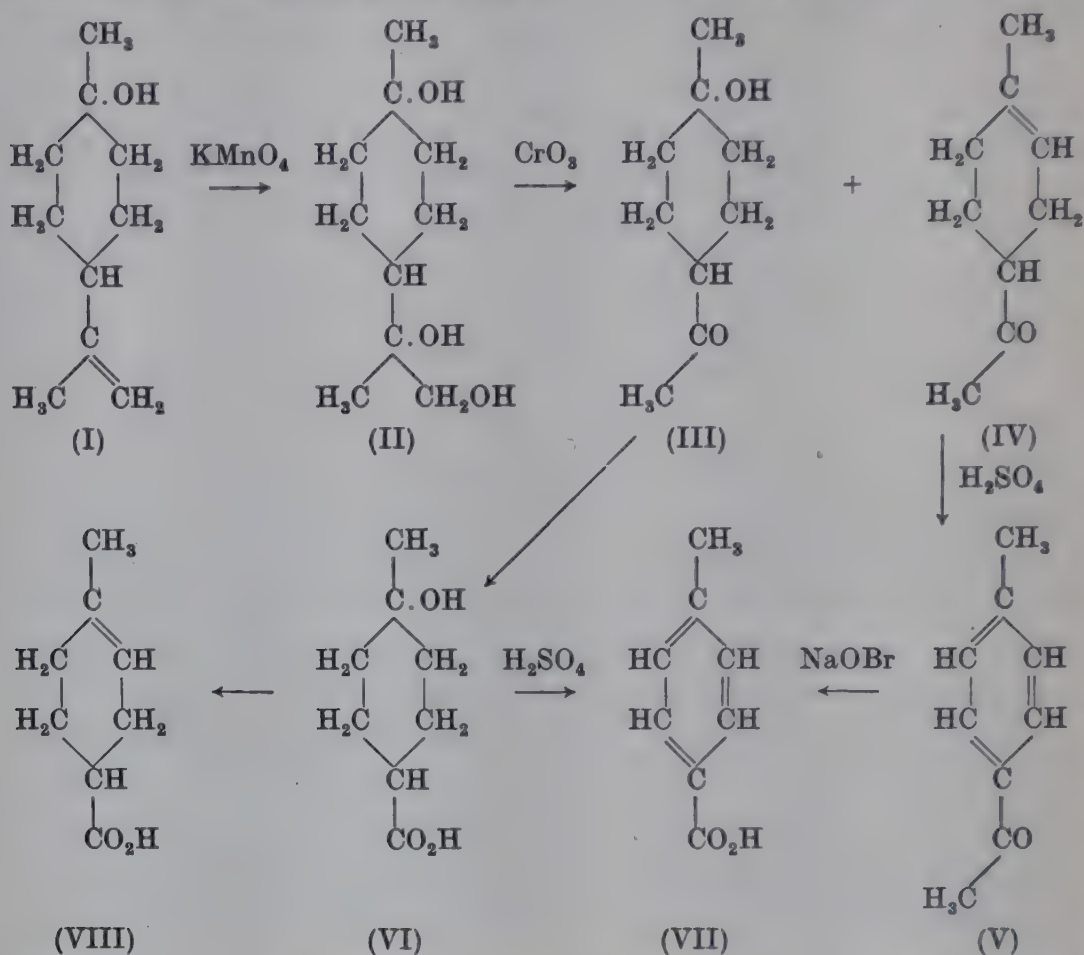
By the action of concentrated sulphuric acid the unsaturated ketone can be converted into p-tolyl methyl ketone (V), whilst oxidation of the hydroxy-ketone (III) with sodium hypobromite yields 1-methylcyclohexan-1-ol-4-carboxylic acid (VI). This hy-

* Ber. 1902, 35, 2148.

† Compt. rend. 1887, 104, 996; Ann. chim. 1887 [vi], 11, 562.

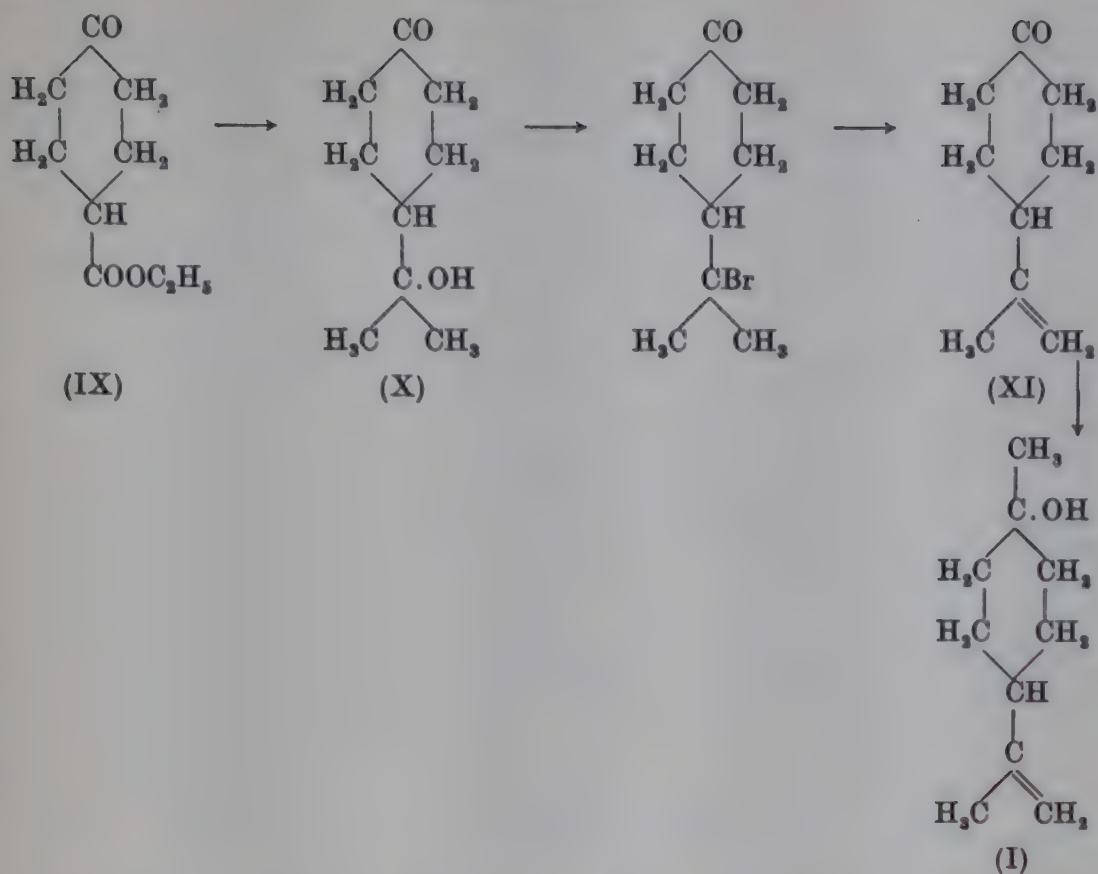
‡ Stephan and Helle, loc. cit.; Wallach and Rahn, Annalen, 1902, 324, 87; Wallach, ibid. 1910, 374, 206; 1911, 381, 90.

droxy-acid, which gives a crystalline *lactone*, m.p. 69–70°, is oxidised by concentrated sulphuric acid to *p*-toluic acid (VII).



Whilst these degradation products leave little doubt as to the constitution of the parent alcohol, its synthesis, which was accomplished by W. H. Perkin, jun.,* in the course of that of α -terpineol, is of great interest. It may be mentioned that incidentally Perkin also synthesised the two acids represented by formulae (VI) and (VIII). By the action of methyl magnesium iodide on *ethyl cyclohexan-4-one-carboxylate* (IX) the *hydroxy-ketone* (X), b.p. 177–180°/100 mm., was obtained and this, by treatment with hydrogen bromide followed by an alcoholic solution of potassium hydroxide, gave the unsaturated ketone, 4-isopropenylcyclohexan-1-one (XI). When this ketone was treated with methyl magnesium iodide, β -terpineol (I) was obtained, which was identified by conversion into the characteristic *phenylurethane*, m.p. 83–85°.

* *J.C.S.* 1904, 85, 670.



β -Terpineol melts at $32-33^\circ$, b.p. $209-210^\circ/752$ mm., $d_{20}^{20} 0.919$, $n_D^{20} 1.4747$; it has a strong odour of hyacinths. The alcohol should exist in *cis-trans*-modifications, but only one form has been described. It can be characterised by the preparation of the *phenylurethane*, m.p. 85° , referred to above.

A further interesting synthesis of the alcohol has been described by Wallach,* who has shown that the unsaturated ketone (IV) when treated with methyl magnesium iodide gives β -terpineol.

On catalytic hydrogenation,[†] the alcohol is converted into *p-menthan-1-ol* (XII), a substance first prepared by Baeyer[‡] by the hydration of *carvomenthene* (Δ^1 -*p-menthene*) (XIII).

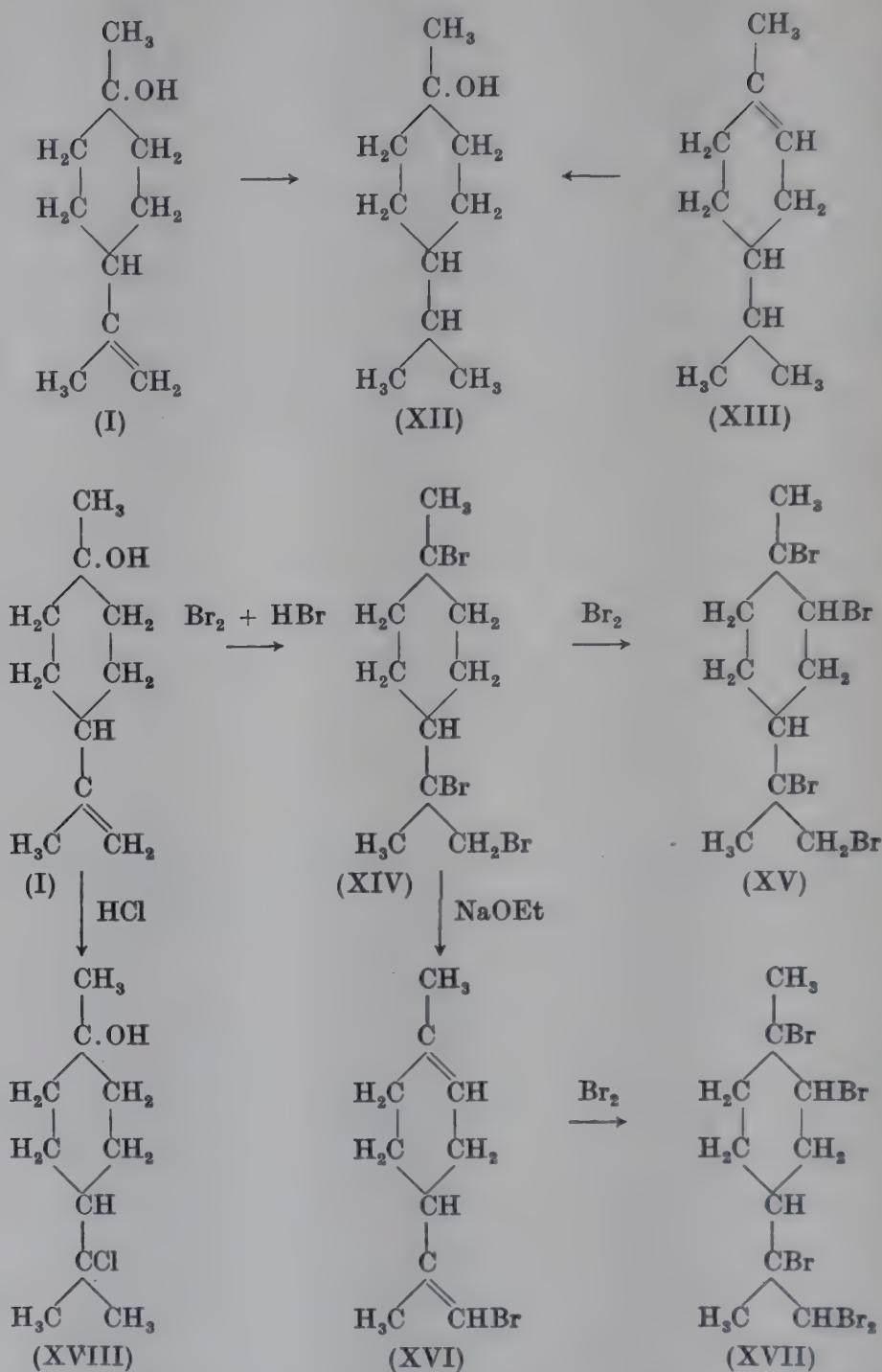
When β -terpineol is treated in acetic acid solution with one mole of bromine and the product then allowed to react with hydrogen bromide, Wallach[§] showed that a crystalline tribromide, 1:8:9-*tribromo-p-menthane* (XIV), m.p. 67° , is formed, which, by the further action of bromine, gives *dipentene tetrabromide*.

* *Annalen*, 1917, **414**, 206.

‡ *Ber.* 1893, **26**, 2270.

† Wallach, *ibid.* 1911, **381**, 58.

§ *Annalen*, 1902, **324**, 82.



If the tribromide is treated with sodium ethoxide, it yields a liquid *monobromide* (XVI), b.p. 105–110°/10 mm., from which on bromination the *pentabromide* (XVII), m.p. 137°, can be prepared.

By the action of an excess of halogen acids on the alcohol the dipentene dihalogenides are obtained, but, if only one mole

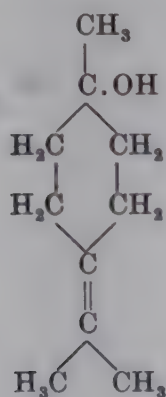
of hydrogen chloride in alcoholic solution is used, a *chlorohydrin* (XVIII), m.p. 74–75°, can be isolated, which with alkalis gives *cis*-terpin.*

By hydration with dilute sulphuric acid terpin hydrate is obtained, the reaction proceeding according to Wallach[†] much more rapidly than is the case with α -terpineol.

β -Terpineol nitrosochloride[‡] melts at 102–103° and does not react very readily with bases, the most satisfactory derivative being the *nitrolanilide*, m.p. 110°. The *nitrosate*, m.p. 125°, and the *nitrosite*, m.p. 78°, have also been prepared. By the action of alkali on the nitrosochloride a hydroxy-oxime is obtained, which cannot, however, be readily purified. When the oxime is hydrolysed with oxalic acid it yields, according to Wallach and Schmitz,[§] an aldehyde, whilst with mineral acids a ketone is formed. The constitution of these two substances has not been determined.

γ -TERPINEOL

($\Delta^{4(8)}$ -p-Menthen-1-ol or
1-Methyl-4-isopropylidenecyclohexan-1-ol)



The occurrence in nature of the alcohol, γ -terpineol, has not been definitely proved, but according to Simonsen^{||} it probably occurs in small quantity in the essential oil from the leaves of *Cupressus torulosa* Don.

* Wallach, *Annalen*, 1906, **350**, 158.

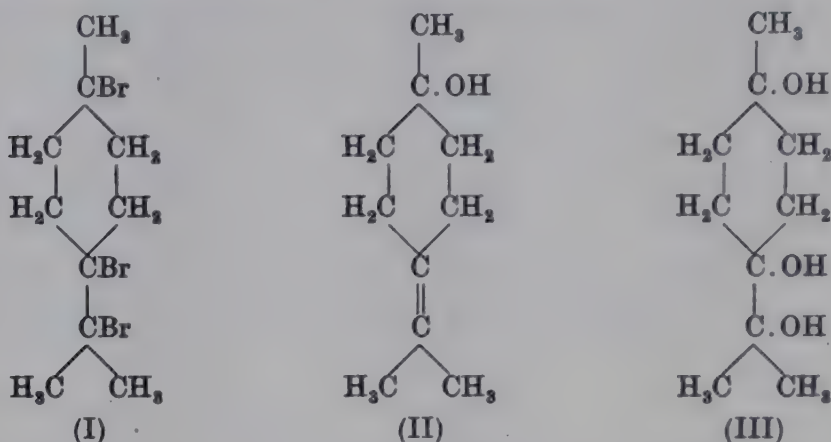
† *Ibid.* 1908, **360**, 101.

‡ Stephan and Helle, *loc. cit.* p. 2150; Wallach and Schmitz, *Annalen*, 1906, **345**, 128.

§ *Annalen*, 1906, **345**, 128.

|| *Ind. For. Rec.* 1923, **10**, 1.

γ -Terpineol was prepared in a pure state by Baeyer and our knowledge of its chemistry is due almost entirely to his investigations. He showed in 1894* that when 1:4:8-tribromo-p-menthane (I), the preparation of which is described on p. 170, was reduced with zinc dust in acetic acid solution, the acetate of an unsaturated alcohol was formed which on hydrolysis gave a new crystalline alcohol, γ -terpineol (II).



Shortly afterwards† he showed that it was present also in the mixture of alcohols which results from the dehydration of *cis*-terpin with either phosphoric or oxalic acids. The evidence on which the constitutional-formula for γ -terpineol is based has already been discussed (p. 170) and need not be recapitulated here.

γ -Terpineol crystallises from ether in thick prisms, m.p. 68–70°; the boiling-point of the alcohol does not appear to have been determined, although Baeyer remarks that it can be distilled without decomposition. It resembles α -terpineol in odour.

Apart from the early investigations of Baeyer and his collaborators, the properties of the alcohol have been little studied; probably the most suitable derivative for its characterisation is the *dibromide*, m.p. 114–115°‡

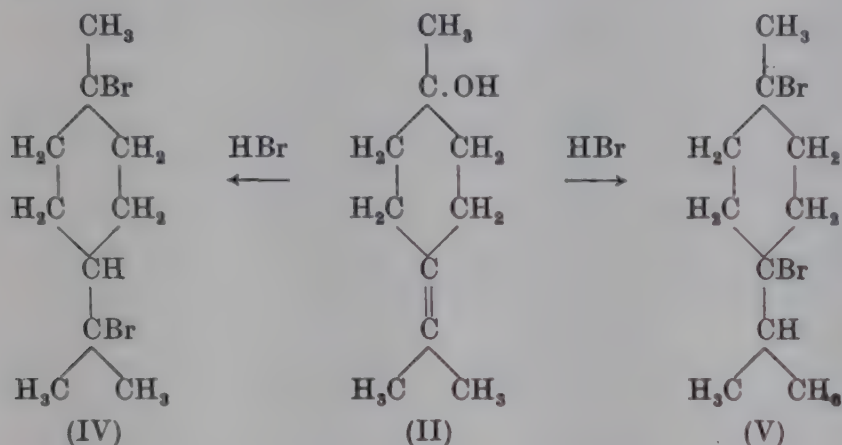
The action of reducing agents on the alcohol has not been investigated, but, on oxidation with potassium permanganate, it gives in excellent yield the glycerol, p-menthane-1:4:8-triol (III), m.p. 110–112°, which can be converted into the tribromide (I) by the action of hydrogen bromide.

* *Ber.* 1894, 27, 443.

† *Ibid.* 1894, 27, 815.

‡ Baeyer and Blau, *ibid.* 1895, 28, 2296.

On treatment with bromine in alcohol-ether solution, a dibromide is formed which crystallises in needles, m.p. 114–115°, and yields with hydrogen bromide the above-mentioned tribromide. According to Baeyer, when the alcohol in acetic acid is treated with hydrogen bromide, the *trans*-dipentene dihydrobromide (IV) is obtained; this reaction is, however, probably influenced by the conditions under which it is performed, since Wallach* has shown that terpinene dihydrobromide (V) is also formed, the addition of the halogen acid to the ethylenic linkage taking place in both possible directions.



The hydration of γ -terpineol with sulphuric acid (1 per cent.) proceeds with remarkable facility, yielding a mixture of *cis*- and *trans*-terpins,[†] the same products being also obtained by the action of alkali. As has been pointed out by Wallach, γ -terpineol is the only one of the three terpeneols which on hydration yields both *cis*- and *trans*-terpins. On dehydration with formic acid terpinolene is obtained.[‡]

Baeyer[§] prepared from the alcohol a blue nitrosochloride, which does not appear to have been crystallised.

From γ -terpenyl acetate, b.p. 110–120°/16 mm., a number of interesting derivatives have been prepared.^{||} With bromine in alcohol-ether solution it gives a *dibromide*, m.p. 103°, from which the tribromide (I) can be obtained by the action of hydrogen bromide. Of special importance are the monomolecular *nitrosochloride* and *nitrosobromide*, which can be readily prepared by

* *Annalen*, 1906, **350**, 160.

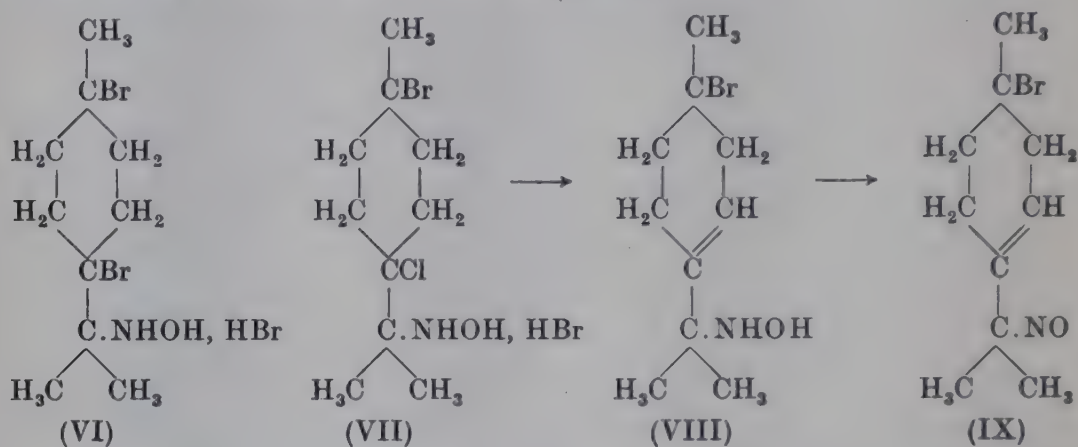
† Wallach, *Ber.* 1907, **40**, 578.

‡ Wallach, *Annalen*, 1909, **368**, 11.

§ *Ber.* 1894, **27**, 441.

|| Baeyer, *ibid.* 1894, **27**, 445; Baeyer and Villiger, *ibid.* 1895, **28**, 652; Baeyer and Blau, *ibid.* p. 2292.

treatment of an alcoholic solution of the acetate with sodium nitrite in the presence of the appropriate halogen acid. The former crystallises from alcohol in blue leaflets, m.p. 82° , and the latter in blue needles, m.p. $81-82^{\circ}$. The nitrosobromide behaves in a somewhat remarkable manner on treatment with hydrogen bromide in acetic acid solution, the halogen acid acting both as a substituting and reducing agent; the *hydroxylamine hydrobromide* (VI) is obtained, the analogous chloride (VII) being formed from the nitrosochloride.



Both these substances give on treatment with alkali the unsaturated *base* (VIII), m.p. 102° , which gives with nitrous acid the *nitroso-derivative* (IX), m.p. $138-139^{\circ}$.

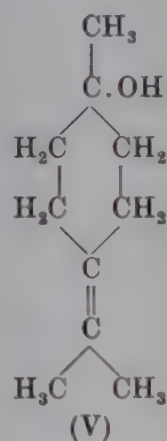
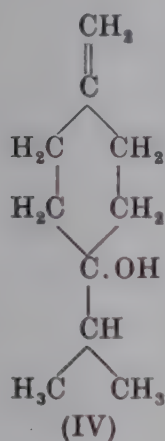
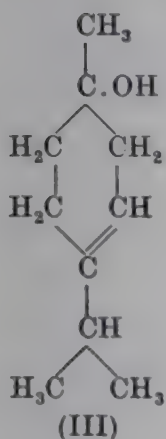
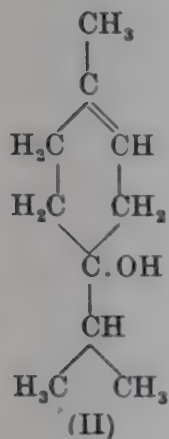
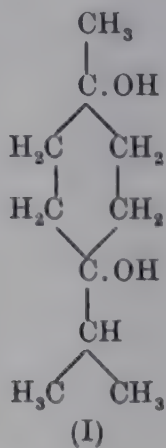
Attention may finally be directed to the conversion of γ -terpenyl acetate into terpinolene by the action of quinoline (compare p. 170).

THE TERPINENOLS

The alcohols, $\text{C}_{10}\text{H}_{18}\text{O}$, to which the term, *terpinenol*, is applied, are derived from terpinene-terpin (1:4-terpin) (I) by the loss of one molecule of water, and they bear therefore the same relationship to this dihydroxy-*p*-menthane as do the terpeneols to terpin.

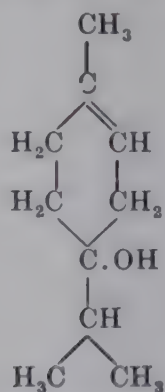
There are four possible alcohols derivable from terpinene-terpin, which are represented by formulae (II), (III), (IV) and (V). The alcohol represented by (V) is γ -terpineol (p. 271), which is related therefore to both terpin and terpinene-terpin. Of the three remaining alcohols only the one represented by (II),

terpinen-4-ol, has been found in nature. *Terpinen-1-ol* (III) has been found in commercial terpineol, whilst the alcohol (IV) has not been described.



TERPINEN-4-OL

(Δ^1 -p-Menthen-4-ol or 1-Methyl-4-isopropyl- Δ^1 -cyclohexen-4-ol)

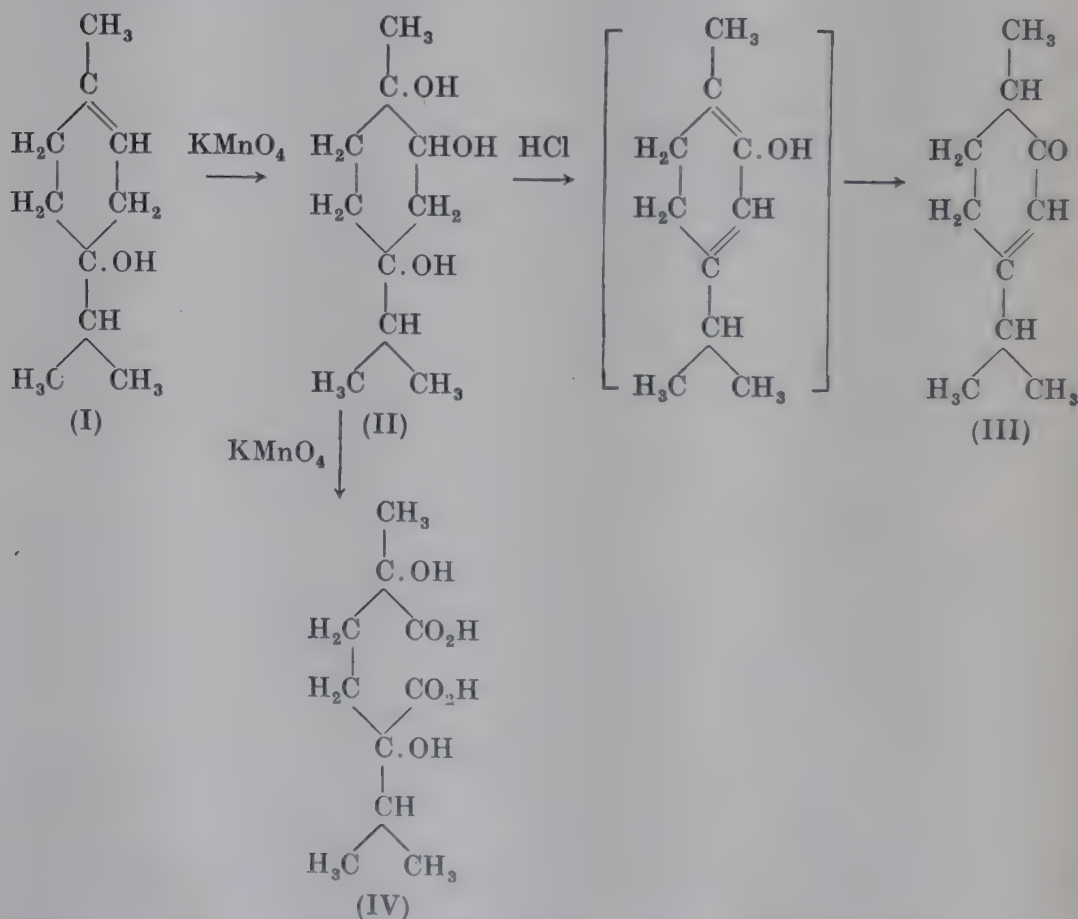


In 1887 Weber* noted the presence in cardamom oil (from the seeds of *Elettaria major* Smith) of a dextrorotatory alcohol,

* *Annalen*, 1887, 238, 98.

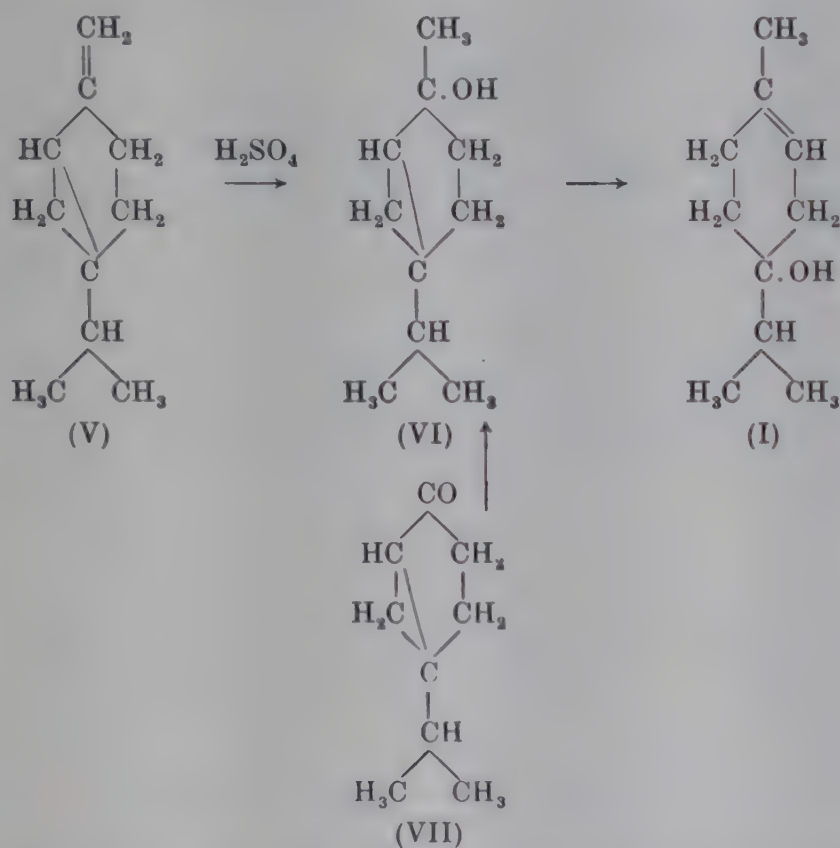
which did not appear to be identical with α -terpineol; it was not, however, until many years later that Wallach* showed it to be identical with the alcohol present in majoram oil (from *Origanum Majorana* L.). The alcohol has since been found to occur in a number of other essential oils, the more important of which are the oils of cypress and nutmegs.

In the course of the investigations referred to above Wallach determined the constitution of the alcohol. On oxidation with dilute potassium permanganate solution, it yields a *glycerol*, m.p. 128–129°, which must be *p-menthane-1:2:4-triol* (II), since on warming with dilute hydrochloric acid it gives carvenone (III); whilst on further oxidation it is converted into $\alpha\delta$ -*dihydroxy- α -methyl- δ -isopropyladipic acid* (IV), identical with the acid obtained by the oxidation of α -terpinene (p. 178). The formation of these products can only be explained if the alcohol has the constitution represented by (I).



* *Annalen*, 1906, **350**, 168; 1907, **356**, 206; *Ber.* 1907, **40**, 596.

Since the alcohol does not yield any crystalline derivatives from which it can be regenerated, its separation from essential oils and its purification are not readily effected. It can be obtained most conveniently by the hydration of the dicyclic hydrocarbon, *sabinene* (V), with mineral acids* or formic acid.† In the latter reaction the formate of the alcohol is obtained. The hydration of the alcohol proceeds probably with the intermediate formation of *sabinene hydrate* (VI) since this substance, which can be prepared synthetically from *sabina ketone* (VII), yields *terpinen-4-ol* on hydration.



In view of the ease with which sabinene can be hydrated to *terpinen-4-ol*, it is possibly not without significance that this hydrocarbon is found in all the oils in which the alcohol occurs.

Only *d*-*terpinen-4-ol* has been found in nature, the *dl*-modification having been prepared synthetically. It is an oil having an odour resembling that of α -*terpineol* and it remains liquid even at low temperatures. The following constants have been

* Wallach, *Annalen*, 1907, **356**, 215; 1908, **360**, 98.

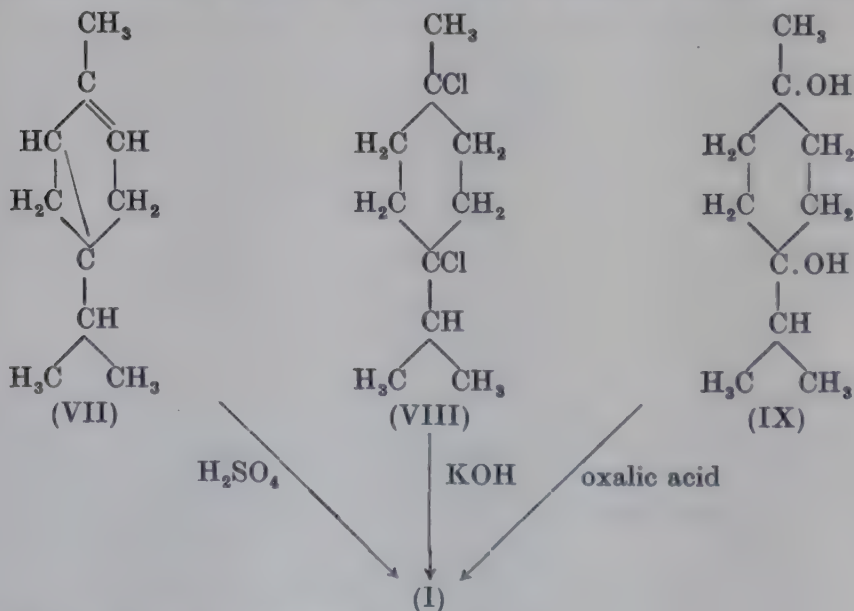
† Semmler, *Ber.* 1906, **39**, 4421.

observed for the *d*- and *dl*-forms: *d*-, b.p. 209–212°, d^{19}_D 0.9265, n^{19}_D 1.4785, $\alpha_D + 25.2^\circ$; *dl*-, b.p. 212–214°, d 0.929, n_D 1.4803.

Terpinen-4-ol is difficult to identify and it is probably most readily characterised by oxidation to the glycerol referred to above, and by its conversion into terpinene dihydrochloride on treatment with hydrogen chloride.

In addition to the methods to which reference has been made, the alcohol can be prepared by the hydration of α -thujene (VII)* and by the action of dilute alkali on *terpinene dihydrochloride* (VIII),† or from *terpinene-terpin* (IX) by treatment with oxalic acid.

With the halogen acids terpinen-4-ol yields the corresponding dihalogenides, whilst, on hydration with dilute sulphuric acid, terpinene-terpin (IX) is formed, a reaction which, however, only proceeds very slowly. The action of phenyl isocyanate was originally stated to result only in dehydration to a hydrocarbon, probably α -terpinene, but according to Nagai‡ it gives a *phenyl-urethane*, m.p. 71–72°. Penfold§ has shown that it yields a highly characteristic *naphthylurethane*, m.p. 104–105°. According to the same author it also gives a crystalline *nitrosochloride*, m.p. 115–116°.|| A *nitrolpiperidide* (α -form, m.p. 155–156°; β -form, m.p. 181–182°) has been prepared by Kafuku, Nozoe and Hata.¶



* Wallach, *Annalen*, 1908, **360**, 97.

† Wallach, *ibid.* 1906, **350**, 155; 1907, **356**, 216.

‡ Beilstein, 1st Suppl., vol. vi, p. 40.

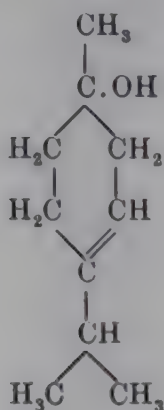
§ *J. Proc. Roy. Soc. New South Wales*, 1926, **59**, 313.

|| See also Hancox and Jones, *Proc. Roy. Soc. Queensland*, 1939, **50**, 40.

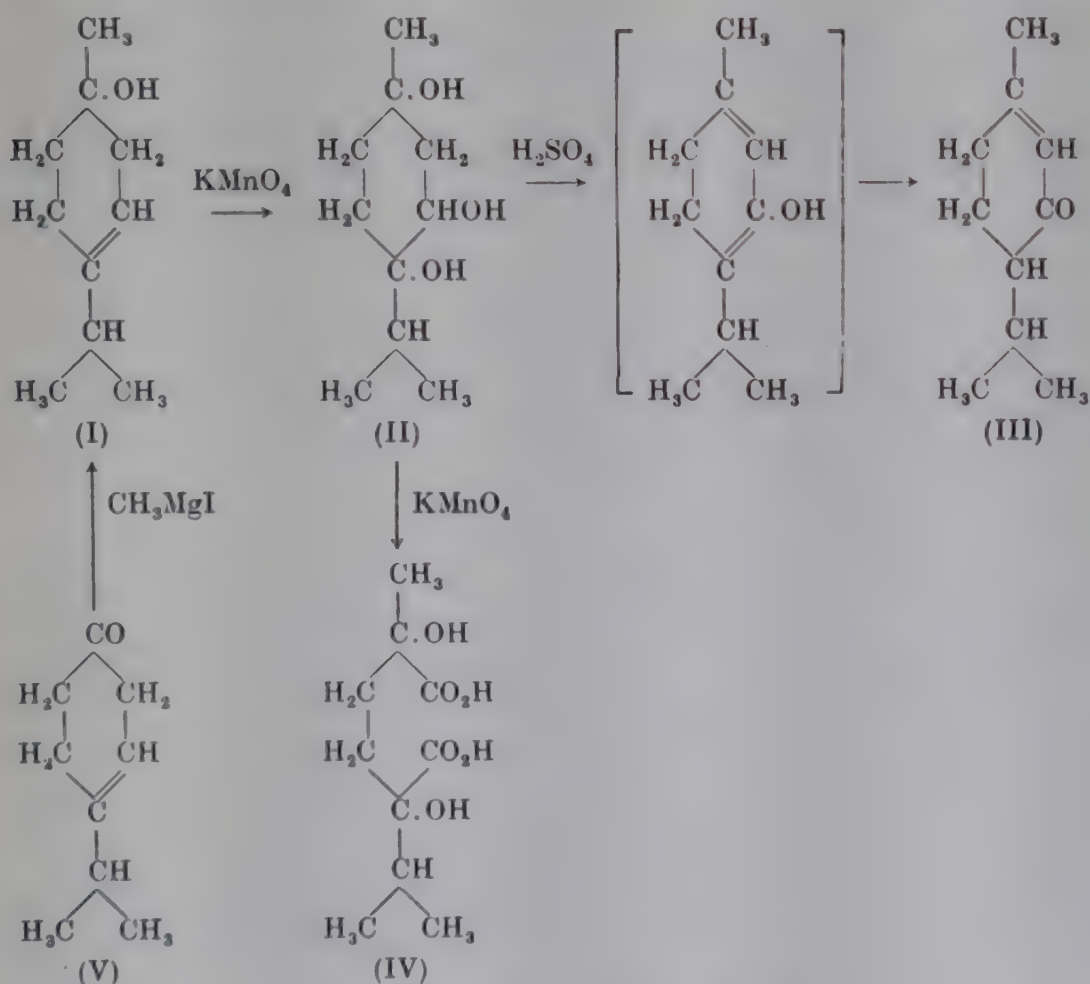
¶ *J.C.S. Japan*, 1934, **55**, 244.

TERPINEN-1-OL

(Δ^3 -p-Menthen-1-ol or 1-Methyl-4-isopropyl- Δ^3 -cyclohexen-1-ol)



Terpinen-1-ol, which does not occur in nature, was separated by Wallach* from the low boiling fraction of commercial terpeneol.



* *Annalen*, 1907, **356**, 218; 1908, **362**, 269.

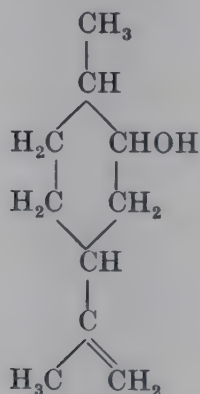
The constitution of the alcohol (I) was determined by its oxidation with dilute potassium permanganate, when, in cold dilute solution, it yields a *glycerol*, m.p. 120–121°, which on further oxidation gives $\alpha\delta$ -*dihydroxy- α -methyl- δ -isopropyladipic acid* (IV). The glycerol was identified as *p-menthane-1:3:4-triol* (II) by its conversion on treatment with dilute sulphuric acid into *dl-piperitone* (III).

The constitution given to the alcohol was confirmed by its synthesis by Wallach and Heyer,* who prepared it by the action of methyl magnesium iodide on 4-isopropyl- Δ^3 -cyclohexen-1-one (V).

Terpinen-1-ol is an oil, b.p. 208–210°, d^{18° 0.9265, $n_D^{18^\circ}$ 1.4781, which does not crystallise at a low temperature. With hydrogen chloride in acetic acid solution it yields terpinene dihydrochloride.

DIHYDROCARVEOL

($\Delta^{8(9)}$ -*p-Menthen-2-ol* or 1-Methyl-4-isopropenylcyclohexan-2-ol)



Although dihydrocarveol, $C_{10}H_{18}O$, was prepared by Leuckart† in 1887, its occurrence in nature was first recorded by Schimmel and Co.‡ in 1905, who separated it from oil of caraway (from the fruits of *Carum carui* L.).

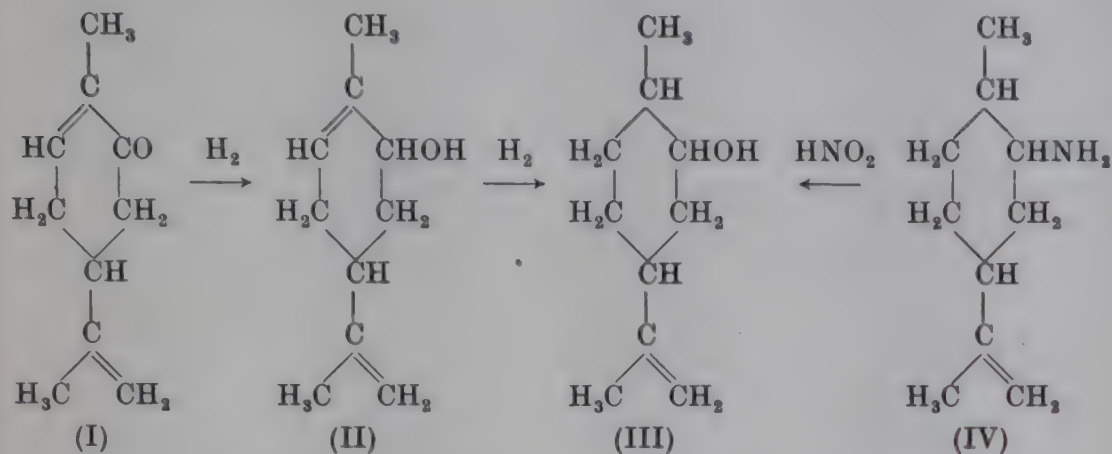
By the reduction of carvone (I) with sodium and alcohol, Leuckart obtained an alcohol, which he characterised by the preparation of a crystalline *phenylurethane*. He erroneously considered this alcohol to be *carveol* (II), but two years later, in

* *Annalen*, 1908, 362, 280.

† *Ber.* 1887, 20, 114.

‡ *Schimmel's Report*, 1905, Apr. p. 20.

collaboration with Lampe,* he corrected this mistake and showed that it had the empirical formula $C_{10}H_{18}O$ and that it was in fact *dihydrocarveol* (III).



The alcohol was subsequently investigated by Wallach,[†] who found that it could be prepared, not only by the reduction of carvone, but also by the action of nitrous acid on *dihydrocarvylamine* (IV), a substance which was formed when carvone was heated with ammonium formate under pressure.

The determination of the constitution of dihydrocarveol was due mainly to the important investigations of Wallach[‡] and of Tiemann and Semmler.[§] With the acceptance of (I) as the correct representation of carvone (see p. 395) it was obvious that for the alcohol, in the absence of isomerisation, only two formulae, (III) and (III a), were possible. An investigation of the oxidation products showed that formula (III) must be correct. On oxidation of the alcohol in ice-cold solution with potassium permanganate a *glycerol* is obtained; this *p*-menthane-triol must be represented by either (V) or (V a), depending upon the constitution of the parent alcohol. Since, however, on further oxidation with chromic acid a *hydroxy-ketone*, $C_9H_{16}O_2$, m.p. $58-59^\circ$, is obtained, it follows that the glycerol can only have formula (V). The hydroxy-ketone must therefore be 1-methyl-4-acetylcyclohexan-2-ol (VI), and this was confirmed by its oxidation by sodium hypobromite to 1-methylcyclohexan-2-ol-4-carboxylic acid (VII), m.p. 153° , from which by dehydrogenation *hydroxy-p-toluic acid* (VIII) was prepared.

* *Dissert. Göttingen*, 1889. † *Ber.* 1891, **24**, 3984; *Annalen*, 1893, **275**, 111.

‡ *Annalen*, 1893, **275**, 155; **277**, 151.

§ *Ber.* 1895, **28**, 2142.

Tschugaev* was successful in separating *d*-dihydrocarveol (and *l*-dihydrocarveol) into two isomerides, only one of which, however, was obtained pure. Although *d*-methyl dihydrocarvylxanthate is a yellow oil, its amide, $C_{10}H_{17}OCSNH_2$, is partially crystalline and can be separated by light petroleum into *d*- α -dihydrocarvylxanthamide, m.p. $62.5-63.5^\circ$, $[\alpha]_D + 135.1^\circ$ (in benzene), and a liquid isomeride, β -dihydrocarvylxanthamide. (The corresponding *l*- α -dihydrocarvylxanthamide has m.p. $62-63^\circ$, $[\alpha]_D - 138.89^\circ$, whilst the *dl*-form has m.p. $95.5-96^\circ$.) Hydrolysis of the crystalline amide with potassium hydroxide gives *d*- α -dihydrocarveol, b.p. $222.5-223^\circ/749$ mm., $d_4^{20} 0.9204$, $n_D^{20} 1.4782$, $[\alpha]_D + 33.86^\circ$; the β -dihydrocarveol, from the liquid isomeride, was probably not homogeneous and had the following constants: b.p. $120^\circ/20$ mm., $d_4^{20} 0.9266$, $n_D^{20} 1.4809$, $[\alpha]_D + 7.64^\circ$. More recently, Johnston and Read† have prepared *d*-dihydrocarveol by the reduction of *d*-carvone with sodium and alcohol. This product, which is probably identical with that described by Tschugaev, has b.p. $107^\circ/15$ mm., $d_4^{16} 0.9223$, $n_D^{16} 1.4784$, $[\alpha]_D^{16} + 34.2^\circ$. The *p*-nitrobenzoate has m.p. 37° , $[\alpha]_D + 52.5^\circ$ in chloroform, and the 3:5-dinitrobenzoate, m.p. 122° , $[\alpha]_D + 55.2^\circ$ in chloroform. On hydrogenation it yields *d*-carvomenthol (see p. 251). They also prepared *l*-neodihydrocarveol, by the reduction of carvone with zinc and potassium hydroxide and also by the reduction of *l*-dihydrocarvone with aluminium isopropoxide. This isomer has b.p. $102^\circ/18$ mm., $n_D^{14} 1.4812$, $\alpha_D^{14} - 33.2^\circ$. The *p*-nitrobenzoate, m.p. 107° , shows $[\alpha]_D + 14.9^\circ$ in chloroform, and the 3:5-dinitrobenzoate, m.p. 138.5° , $[\alpha]_D + 6.8^\circ$ in chloroform. On hydrogenation the alcohol gives *l*-neocarvomenthol.

Considerable attention has been devoted to the action of oxidising agents on dihydrocarveol and the action of potassium permanganate has already been discussed. With chromic acid Wallach‡ found that the secondary alcohol group only was attacked with formation of the corresponding ketone, dihydrocarvone, whose rotatory power is opposite in sign to that of the alcohol from which it is prepared. Wallach and his collaborators§ have carefully investigated the properties of the glycerol,

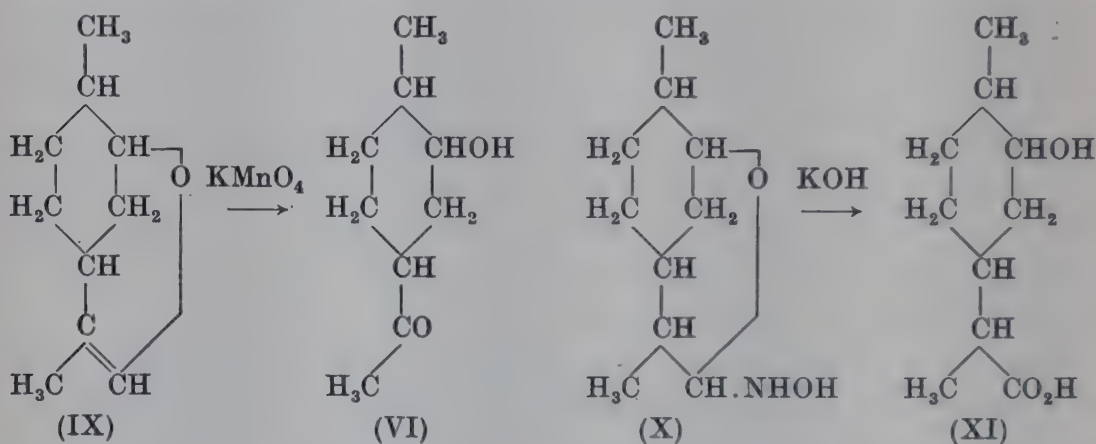
* Ber. 1902, 35, 2479.

† J.C.S. 1934, 233.

‡ Annalen, 1893, 275, 115.

§ Ibid. 1893, 277, 151; 1894, 279, 386; 1902, 324, 91.

p-menthane-2:8:9-triol (V), obtained by the oxidation with potassium permanganate. With dilute sulphuric acid, it is converted into an unsaturated *oxide*, b.p. 95°/20 mm., *d* 0.9647, *n*_D 1.4844; this oxide gives a crystalline *dibromide*, m.p. 58°, and with hydroxylamine it yields two isomeric *hydroxylamino*-derivatives, m.p. 111–112° and 164–165°, respectively. There can be no doubt that this oxide has formula (IX), since, on oxidation with potassium permanganate, it gives a hydroxy-ketone (VI) identical with that formed by the oxidation of the glycerol with chromic acid (p. 281). The hydroxylamino-derivatives must therefore be represented by formula (X), which structure receives support by their hydrolysis with alkali to the *hydroxy-acid* (XI).



According to Dupont,* the autoxidation of dihydrocarveol in the presence of cobalt salts leads to the formation of *tetrahydro-p-tolyl methyl ketone*, a substance which may be regarded as a dehydration product of (VI).

Dihydrocarveol reacts with halogens and halogen acids to yield addition products, which are somewhat unstable and which have not been obtained crystalline. From the liquid *hydrobromide* (XII) (8-bromocarvomenthol) Baeyer and Henrich† prepared by the action of silver acetate, followed by hydrolysis of the resulting acetyl derivative, a crystalline glycol, *p*-menthane-2:8-diol (XIII), m.p. 110.5–112°.

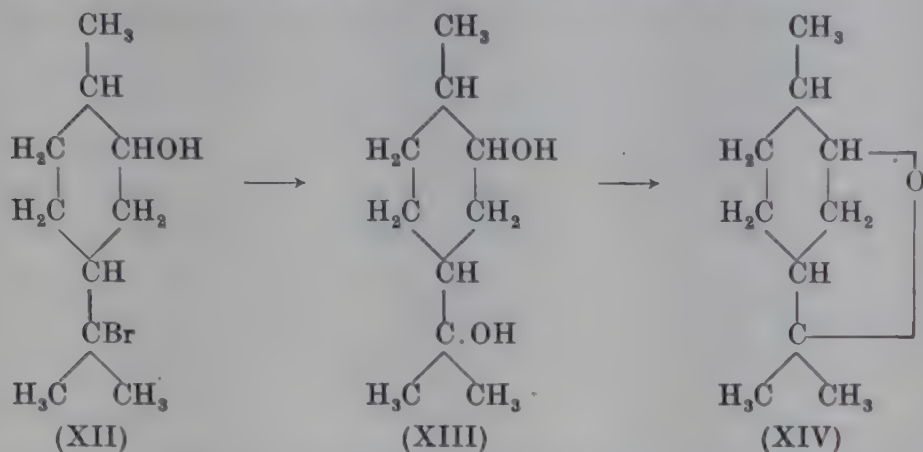
This glycol, together with an isomeride, m.p. 103–104°, is also formed when dihydrocarveol is hydrated with sulphuric acid.‡

* *Ind. chim. belge*, 1940 [2], 11, 3.

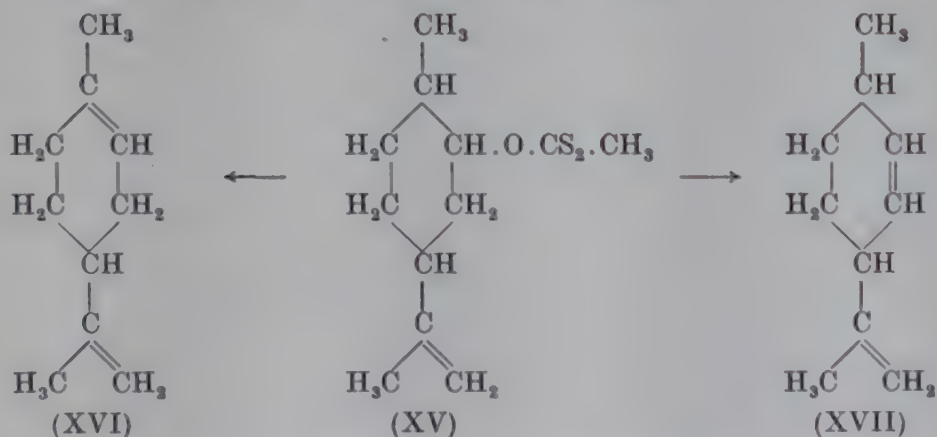
† *Ber.* 1895, 28, 1589.

‡ Rupe and Schlochoff, *Ber.* 1905, 38, 1719; Wallach, *Annalen*, 1908, 360, 102.

These are possibly *cis-trans*-isomerides and when digested with dilute sulphuric acid, they lose water with formation of the oxide, *dihdropinol* (XIV), b.p. 58.25–58.75°/9 mm.*



The conditions governing the conversion of dihydrocarveol into hydrocarbons were first examined by Wallach,[†] who found that dehydration with dilute sulphuric acid led mainly to the formation of α -terpinene. Of greater interest are, however, the experiments of Tschugaev,[‡] who showed that the distillation of *d*-methyl dihydrocarvylxanthate (XV) gave a mixture of *l*-limonene (XVI) and *l*-isolimone (XVII).



l-isoLimonene, b.p. 172.5–173.5°, d_4^{20} 0.8370, n_D 1.4704, $[\alpha]_D$ –140.58°, forms the main product of the reaction. This hydrocarbon does not give a crystalline tetrabromide, but with hydrogen bromide, owing to isomerisation, dipentene dihydrobromide is obtained. The constitution of this hydrocarbon, which

* Wallach prepared two stereoisomeric glycols from pinol hydrate; for details of their properties reference should be made to the original memoir, *Annalen*, 1917, 414, 195.

[†] *Ber.* 1891, 24, 3984; *Annalen*, 1893, 275, 113.

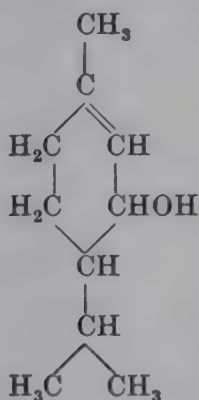
[‡] *Ber.* 1900, 33, 735; 1902, 35, 2479; *J. Russ. Phys. Chem. Soc.* 1904, 36, 988.

according to Mereshkovski* is also formed when the alcohol is heated with boric anhydride at 200° , cannot be regarded as fully established (compare p. 213).

A large number of esters of dihydrocarveol have been described but they do not call for special mention. Hämäläinen† has prepared a β -glucoside, m.p. $164\text{--}165^{\circ}$.

PIPERITOL

(Δ^1 -p-Menthen-3-ol or 1-Methyl-4-isopropyl- Δ^1 -cyclohexen-3-ol)



The secondary alcohol, piperitol, $\text{C}_{10}\text{H}_{18}\text{O}$, does not appear to be widely distributed in nature. *l*-Piperitol was first separated from the oil of *Eucalyptus radiata* by Smith,‡ and has since been found to occur in other eucalyptus oils. *d*-Piperitol was shown by Simonsen§ to be present in small amount in the oil from an unidentified species of *Andropogon* growing in the Etawah District, U.P., India.

According to a recent patent|| *l*-piperitol (I) can most conveniently be prepared in quantity from *l*- α -phellandrene (II). This hydrocarbon on treatment with hydrogen chloride yields piperityl chloride (III), from which by the action of alcoholic sodium hydroxide *l*-piperitol is obtained. The alcohol can be prepared in somewhat better yield by treatment of the chloride with sodium acetate, the resulting acetyl derivative being hydrolysed to the alcohol. The alcohol, $[\alpha]_D -34.2^{\circ}$, was not stereochemically pure.

* *J. Russ. Phys. Chem. Soc.* 1913, **45**, 1687.

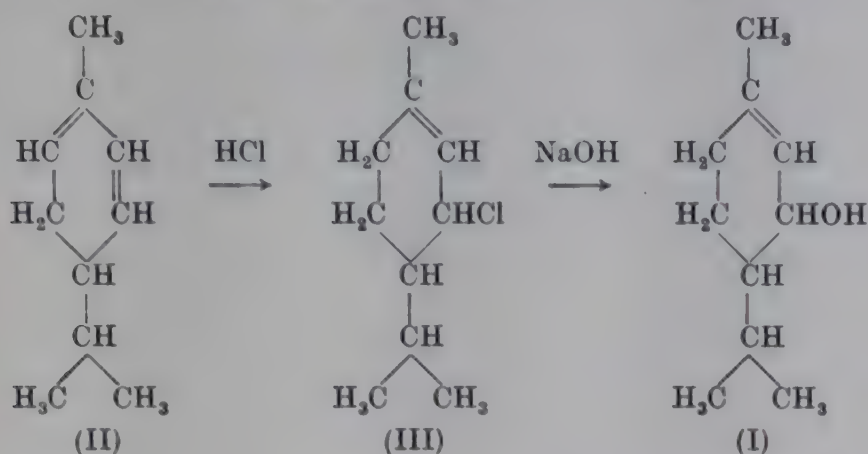
† *Biochem. Z.* 1913, **49**, 398.

‡ Baker and Smith, *Research in the Eucalypts*, 2nd ed. p. 373.

§ *Ind. For. Rec.* 1924, **10**, 161.

|| B.P. 532614, (1941); compare Cuthbertson, Thesis, St Andrews 1946.

It was characterised by the preparation of the crystalline derivative, *triphenylmethyl piperityl ether*, m.p. 132–133°.

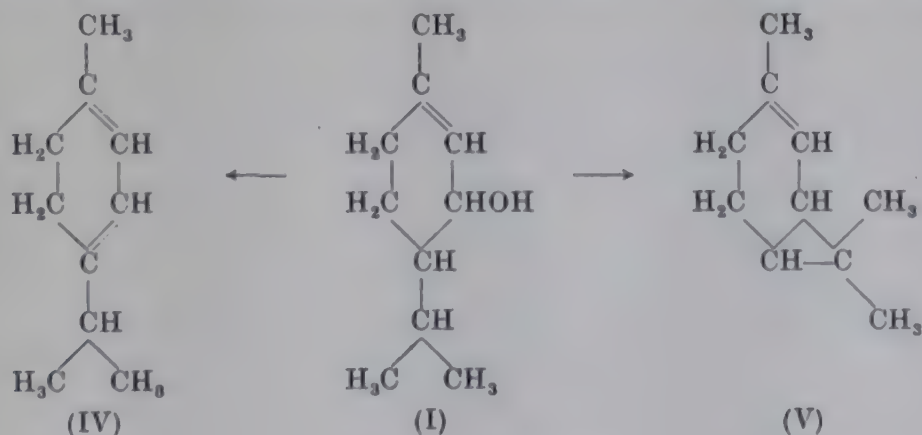


Piperitol is a pleasant smelling, somewhat viscid oil, for which the following constants have been observed: *d*-form, b.p. 165–170°/200 mm., d_{30}^{30} 0.911, n_D^{30} 1.474, $[\alpha]_D + 46.0^\circ$; *l*-form, d^{22} 0.923, n_D^{22} 1.476, $[\alpha]_D - 34.1^\circ$.

The identification of piperitol as Δ^1 -*p*-menthen-3-ol is established by the fact that, on oxidation with chromic acid, it yields piperitone, Δ^1 -*p*-menthen-3-one (p. 359). Oxidation to the ketone provides the most convenient method of characterisation.

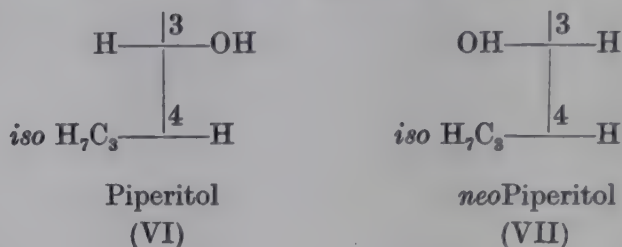
Simonsen has pointed out that piperitol (I) is related in an interesting manner to α -terpinene (IV) and Δ^4 -carene (V), since both these hydrocarbons might be formed by dehydration of the alcohol, and he has shown* that the dehydration of *d*-piperitol with methyl magnesium iodide gives α -terpinene; from *l*-piperitol, an unidentified terpene was obtained.

Since piperitol contains two dissimilar asymmetric carbon



* *Loc. cit.* p. 163.

atoms it can exist in four optically active and two racemic forms. It is probable that none of these has yet been obtained pure, but Read and Walker* have found that the action of moist silver oxide on *l*-piperityltrimethylammonium iodide gives a piperitol which shows the remarkable property of spontaneous loss of water, being largely converted into *d*- α -*phellandrene* (II) when kept at room temperature for several days.



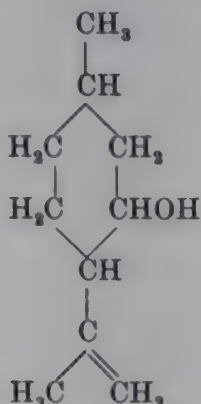
In conformity with the nomenclature adopted in the menthol series (p. 233), this less stable isomer, which has $n_D^{15^\circ}$ 1.4775, $[\alpha]_D + 50.8^\circ$ in alcohol, is termed *d*-*neopiperitol*. It was originally assigned the *trans*-configuration (VI), but in view of the more recent investigations in the menthol field it is almost certainly the *cis*-form (VII), which would lose water by *trans*-elimination. The purest specimen of the *trans*-isomer (VI) so far obtained is probably that prepared† by the reduction of *l*-piperitone with aluminium *isopropoxide*, which gives *l*-piperitol, b.p. 98.5–100.5°/13 mm., $n_D^{19^\circ}$ 1.4776, $[\alpha]_D^{16^\circ} - 24.5^\circ$ in alcohol, which shows no spontaneous loss of water. The 3:5-*dinitrobenzoate* has m.p. 84–85°.

* *J.C.S.* 1934, p. 308; compare Read and Storey, *ibid.* 1930, p. 2770.

† Read and Walker, *loc. cit.*; compare Gibson and Simonsen, *J.S.C.I.* 1930, **49**, 540.

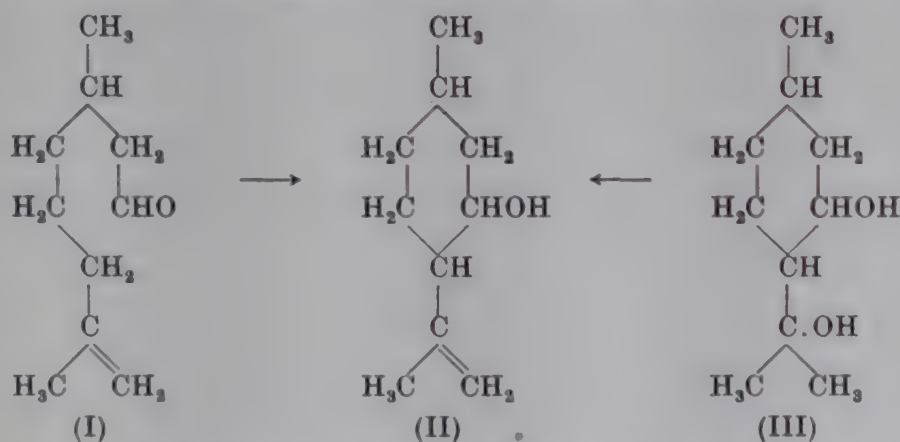
ISOPULEGOL

($\Delta^{8(9)}$ -*p*-Menthen-3-ol or 1-Methyl-4-isopropenylcyclohexan-3-ol)



Although isopulegol, $\text{C}_{10}\text{H}_{18}\text{O}$, has been known for a considerable time, it is only recently that it has been found to occur in nature. According to Penfold* it is present in the essential oil of *Leptospermum liversidgei*, var. B.

As was mentioned on p. 80 the acetyl derivative of the alcohol was prepared by Tiemann and Schmidt† by digestion of the acyclic aldehyde, *citronellal* (I), with acetic anhydride.



Subsequently Semmler‡ found that it could be prepared by the action of acetic anhydride on the enolic form of the aldehyde and by the action of the same reagent on the *glycol* (III).§

Although citronellal is a mixture (p. 72), isopulegol is a homogeneous substance and is undoubtedly represented by formula (II). As was apparently first suggested by Harries and

* *J. Proc. Roy. Soc. New South Wales*, 1932, **65**, 185.

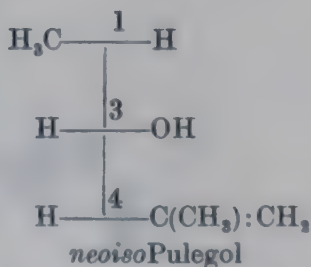
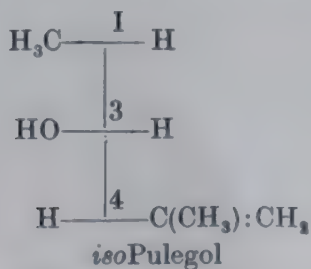
† *Ber.* 1896, **29**, 913; 1897, **30**, 27.

‡ *Ibid.* 1909, **42**, 2016.

§ Compare Barbier and Léser, *Compt. rend.* 1897, **124**, 1309.

Himmelmann,* it is probable that the aldehyde containing the *isopropylidene* group does not undergo cyclisation, since the yield of alcohol never rises above 50 per cent. The constitution of the alcohol follows from the fact that on oxidation with chromic acid it yields *isopulegone*, though some *pulegone* is usually formed at the same time owing to the facile interconversion of these two ketones.

isoPulegol is a colourless oil with an odour reminiscent of that of menthol and has been characterised by the preparation of the *allophanate*, m.p. 219° .† It is a mixture of stereoisomerides, since in the cyclisation of citronellal two additional asymmetric carbon atoms are formed, and theoretically, therefore, *isopulegol* can exist in four stereoisomeric pairs of dextro- and laevo-rotatory compounds. The nature of the stereoisomeric mixture of alcohols obtained from *d*-citronellal was studied by Pickard, Hunter, Lewcock and Pennington.* By fractional crystallisation of the magnesium salts of the hydrogen phthalic esters, they succeeded in isolating two alcohols, which they designated *l-isopulegol* and *d-α-isopulegol*. The former alcohol only was obtained in a state of purity. *l-isoPulegol* had b.p. $94^{\circ}/14$ mm., $d_4^{20^{\circ}}$ 0.9110, $n_D^{20^{\circ}}$ 1.4723, $[\alpha]_{5461} - 25.9^{\circ}$; whilst for *d-α-isopulegol* $d_4^{14.5^{\circ}}$ 0.9172, $[\alpha]_{5461} + 29.3^{\circ}$ was observed. These alcohols differ only in configuration at C_3 , since on hydrogenation they yield *l*-menthol and a somewhat impure *d-neomenthol* respectively. Short and Read,§ by reduction of *d*-pulegone with aluminium *isopropoxide*, have recently prepared pure *d-neoisopulegol*, b.p. $95^{\circ}/17$ mm., $d_4^{25^{\circ}}$ 0.9107, $n_D^{25^{\circ}}$ 1.4686, $\alpha_D + 25.3^{\circ}$ (3:5-dinitrobenzoate, m.p. $138-139^{\circ}$, $[\alpha]_D + 45.0^{\circ}$ in chloroform). On hydrogenation, this gives pure *d-neomenthol*, and it is therefore probable that the *d-α-isopulegol*, mentioned above, was an impure form of *d-neoisopulegol*. On the basis of the configurations assigned to the menthols (p. 242) the two known *isopulegols* may be represented by the following formulae:



* Ber. 1908, 41, 2187.

† J.C.S. 1920, 117, 1248.

† Béhal, Bull. Soc. chim. 1919 [v], 25, 479.

§ Ibid. 1939, p. 1306.

In the sequel, however, the term "*isopulegol*" refers to the mixture of stereoisomerides generally encountered.

In addition to the methods referred to above, *isopulegol* has been obtained by the action of light on citronellal* and also by the action of the Grignard reagent on the aldehyde.†

isoPulegol cannot be reduced by sodium and alcohol,‡ but, as has already been mentioned, this can be done catalytically.

isoPulegol is readily hydrated with dilute sulphuric acid to *p-menthane-3:8-diol* (III), m.p. 75°,§ but, according to Horiuchi,|| if acid of a concentration of 20 per cent. is used, a terpene, C₁₀H₁₆, is formed in addition to the diol. Apart from the allophanate and 3:5-dinitrobenzoate, the only other crystalline derivative of *isopulegol* is the *phosphonic acid*, C₁₀H₁₉O₄P, m.p. 181–182°, which was prepared by Dodge¶ by the action of phosphorus pentoxide on citronellal. The constitution of this body is not known, but, since it cannot be hydrolysed, the PO₃ group is probably attached to the nucleus. On distillation it undergoes decomposition with formation of *isopulegol*. When heated with sodium ethoxide at 210°, Grignard and Dœuvre** have shown that citronellol is formed, conversion into the aldehyde, citronellal, occurring if the cyclic alcohol is distilled over glass wool at 500° at a pressure of 25 mm.

Pickard and his collaborators have prepared a number of the esters of *l-isopulegol* and have studied their rotatory powers.

* Sernagiotta, *Atti R. Accad. Lincei*, 1915 [v], **24**, 850.

† Rupe, *Annalen*, 1914, **402**, 174.

‡ Tiemann and Schmidt, *Ber.* 1897, **30**, 27.

§ Wallach, *Annalen*, 1908, **360**, 102.

|| *Mem. Coll. Sci. Kyoto*, 1928, **11** (A), 171.

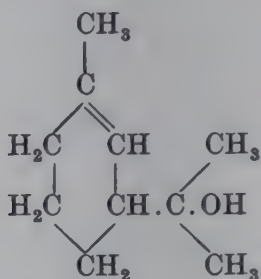
¶ *J. Amer. C.S.* 1915, **37**, 2757.

** *Compt. rend.* 1930, **190**, 1164.

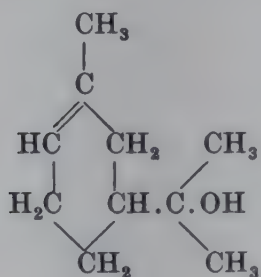
SYLVETERPINEOLS

(CARVETERPINEOLS)*

(Δ^1 -*m*-Menthen-8-ol or 1-Methyl-3-isopropyl- Δ^1 -cyclohexen-8-ol)
(*Dihydrocarvestrenol*)



(Δ^6 -*m*-Menthen-8-ol or 1-Methyl-3-isopropyl- Δ^6 -cyclohexen-8-ol)
(*Dihydroisocarvestrenol*)



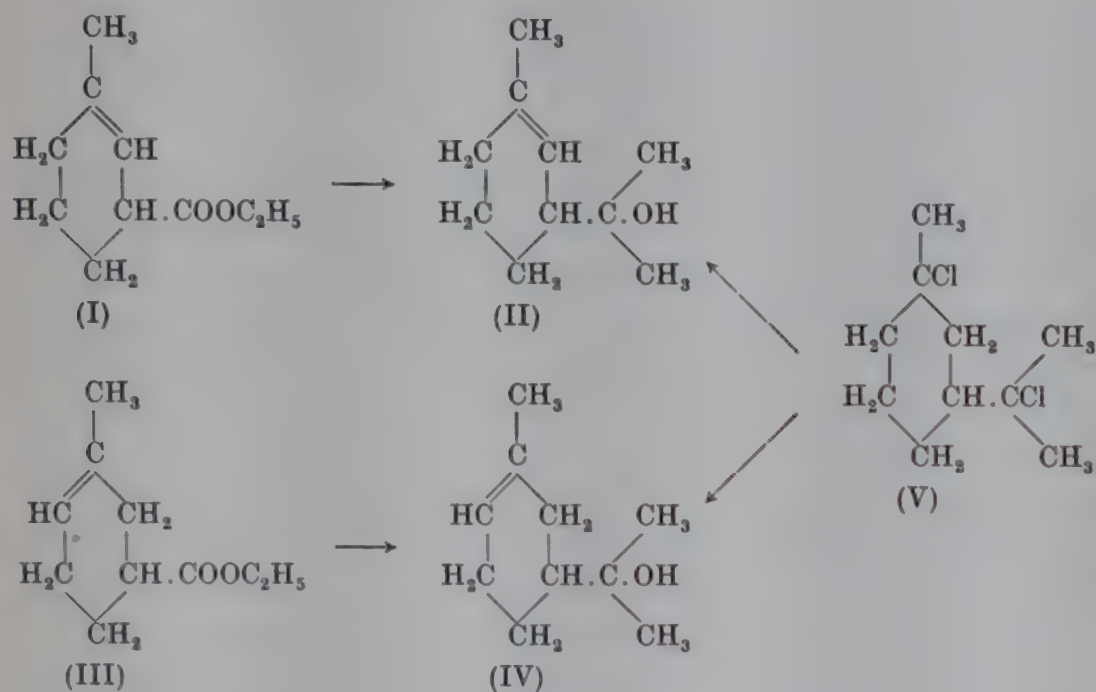
The optically inactive terpeneol, $C_{10}H_{18}O$, of the *m*-cymene series, Δ^1 -*m*-menthen-8-ol, *dihydrocarvestrenol* (II), was synthesised by Perkin and Tattersall[†] by the action of methyl magnesium iodide on ethyl 1-methyl- Δ^1 -cyclohexene-3-carboxylate (I) in 1907, whilst in the following year Fisher and Perkin[‡] prepared the isomeric alcohol, Δ^6 -*m*-menthen-8-ol, *dihydroisocarvestrenol* (IV), from ethyl 1-methyl- Δ^6 -cyclohexene-3-carboxylate (III).

* There are obviously several trivial names which can be given to the terpeneols of the *m*-cymene series. The active terpeneol was called *sylveterpineol* or *sylvestrol* by Haworth, Perkin and Wallach, whilst the racemic alcohols synthesised by Perkin and Tattersall and by Fisher and Perkin were designated *dihydrocarvestrenol* and *dihydroisocarvestrenol* respectively. The names, *carveterpineol* and *carvestrol*, corresponding to *sylveterpineol* and *sylvestrol*, would be equally suitable.

[†] *J.C.S.* 1907, **91**, 483.

[‡] *Ibid.* 1908, **93**, 1887.

Contemporaneously Wallach* prepared the optically active alcohol, *sylveterpineol* (*sylvestrol*), by treatment of sylvestrene dihydrochloride (V) with dilute potassium hydroxide. From its method of preparation, it is obvious that this alcohol may be represented by either (II) or (IV), and as was shown later by Haworth, Perkin and Wallach,† on evidence which has already been summarised on p. 222, the alcohol is actually a mixture of the Δ^1 - and Δ^6 -isomerides.



Although Perkin and his collaborators considered originally that dihydrocarvestrenol and dihydroisocarvestrenol were homogeneous, the later experiments of Haworth and Perkin‡ described on p. 224 have shown that this is not the case. Dihydrocarvestrenol, considered to be the pure Δ^1 -alcohol, must be regarded as a mixture of the Δ^1 - and Δ^6 -isomerides, in which the former is present in predominating amount, whilst the reverse is true for dihydroisocarvestrenol.

The alcohols are viscid oils with an odour resembling that of α -terpineol and the following constants have been observed, the purest and most homogeneous specimens being, in all prob-

* *Annalen*, 1907, 357, 73.

† *J.C.S.* 1913, 103, 1234.

‡ *Ibid.* p. 2227.

ability, the optically active alcohols prepared by Haworth and Perkin:

dl- Δ^1 -*m*-menthen-8-ol (*dihydrocarvestrenol*), b.p. 105–108°/30 mm., * $d_{15}^{15^\circ}$ 0.9257, $n_D^{15^\circ}$ 1.4853.

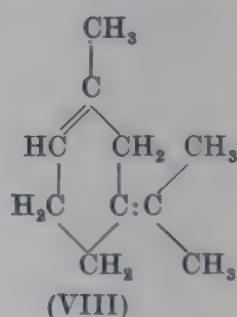
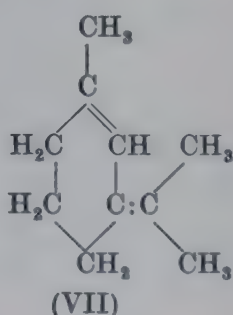
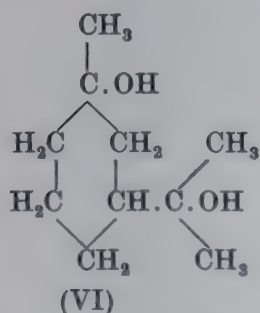
l- Δ^1 -*menthen*-8-ol, b.p. 106–108°/20 mm., $[\alpha]_D - 45.9^\circ$.

dl- Δ^6 -*m*-menthen-8-ol (*dihydroisocarvestrenol*), b.p. 106–107°/20 mm., $d_{20}^{20^\circ}$ 0.9376, $n_D^{15^\circ}$ 1.4871.

d- and l- Δ^6 -*m*-menthen-8-ols, b.p. 106–107°/20 mm., $[\alpha]_D + 1^\circ$, and $[\alpha]_{5461} - 3.46^\circ$ (in ethereal solution, 15 per cent.).

d-*sylveterpineol* (from sylvestrene dihydrochloride), b.p. 214°, d 0.924, n_D 1.4822, $[R_L]_D$ 45.9.

When dissolved in acetic anhydride dihydrocarvestrenol and dihydroisocarvestrenol give with sulphuric acid a violet coloration which changes to an intense methylene blue coloration. On treatment with halogen acids, both alcohols give carvestrene dihydrohalides, but, as already mentioned (p. 222), whereas dihydrocarvestrenol yields carvestrene on dehydration, dihydroisocarvestrenol gives an isomeric hydrocarbon, *isocarvestrene*, the constitution of which has not been determined. On hydration with dilute sulphuric acid, *cis-m*-menthane-1:8-diol (VI) is formed. Dihydroisocarvestrenol can be readily characterised by the preparation of a crystalline *nitrosochloride*, decomposing at 125°. The conversion of the active alcohols into *d*- and *l*-sylvestrenes has been referred to already on p. 226.

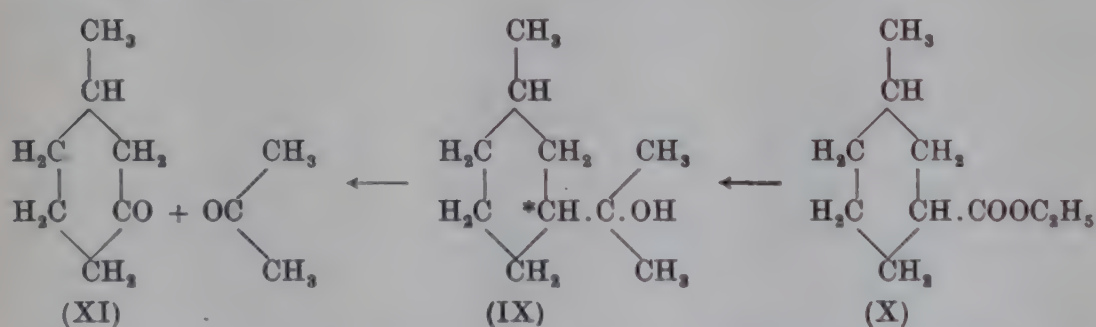


Haworth, Perkin and Wallach, in addition to studying the oxidation of sylveterpineol, investigated also its reactions with other reagents. When digested with a solution of oxalic acid,

* This is probably a misprint for 20 mm.

like terpineol, it loses water with formation of a *hydrocarbon*, b.p. 185°. This hydrocarbon, which was optically inactive, was not obtained pure, being contaminated probably with *m*-cineole, but it was found to absorb oxygen with great rapidity and to resinify very readily. It is probably a mixture of the two *m-terpinolenes* represented by (VII) and (VIII), since, on treatment with hydrogen chloride, it yields carvestrene dihydrochloride.

The catalytic hydrogenation of sylveterpineol, first studied by Wallach,[†] was investigated in greater detail by Haworth, Perkin and Wallach,[‡] who showed that *d-dihydrosylveterpineol* (*d-m-menthan-8-ol*) (IX), b.p. 206–208°, $[\alpha]_D +10.35$, was formed. The *phenylurethane* was prepared and melted at 71–74°. This alcohol is structurally identical with the racemic alcohol prepared by Perkin and Tattersall[§] by the action of methyl magnesium iodide on ethyl 1-methylcyclohexane-3-carboxylate (X).



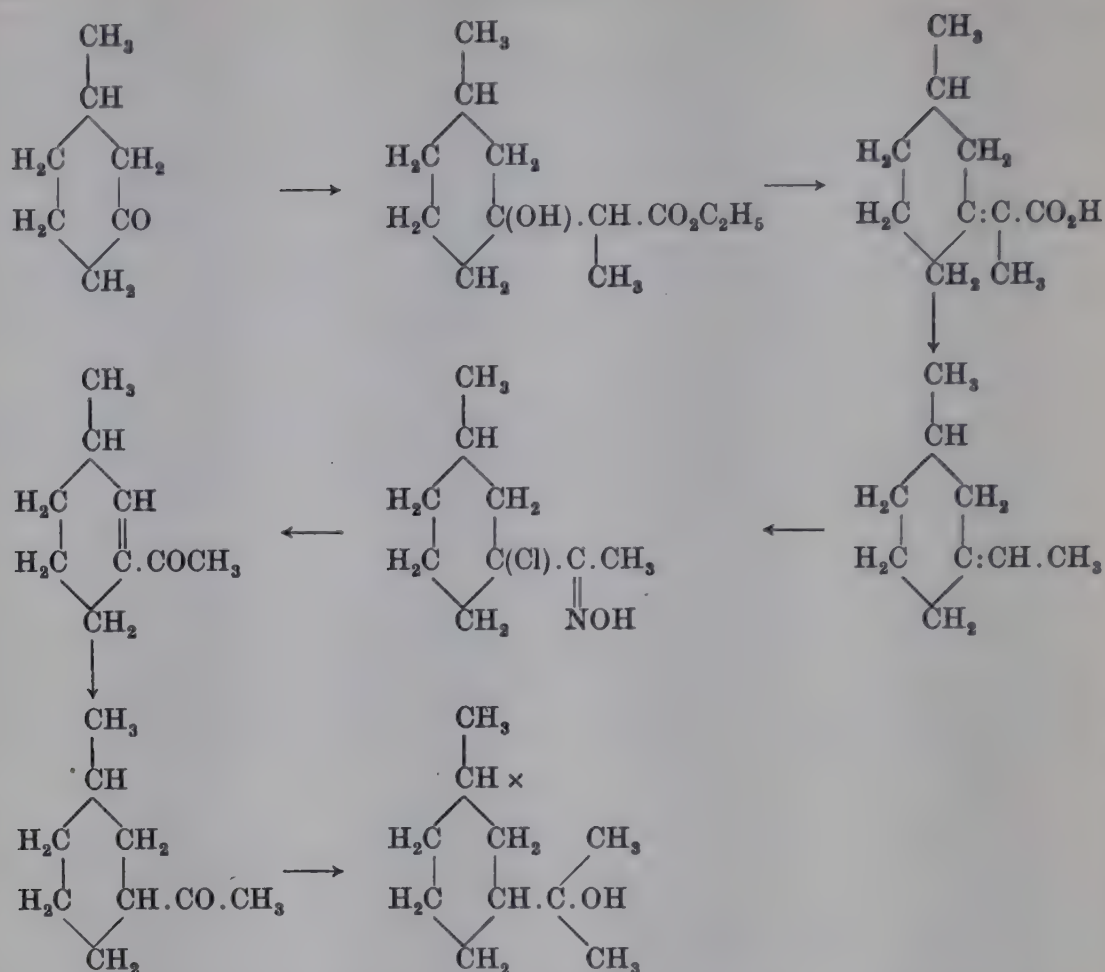
On oxidation with chromic acid, acetone and *dl*-1-methylcyclohexan-3-one (XI) are formed. The formation of the racemic ketone indicates that the dihydrosylveterpineol owes its optical activity to the asymmetric carbon atom (3), indicated by the asterisk in formula (IX), which is readily accounted for by the fact that the other asymmetric carbon atom (1) is formed during the hydrogenation and will therefore be a mixture of *d*- and *l*-forms. Confirmation of this was afforded by a synthesis of a *second d-dihydrosylveterpineol* from *d*-1-methylcyclohexan-3-one prepared from pulegone by the reactions shown schematically on page 296.^{||}

[†] *Annalen*, 1911, 381, 60.

[‡] *J.C.S.* 1913, 103, 1234.

[§] *Ibid.* 1905, 87, 1102.

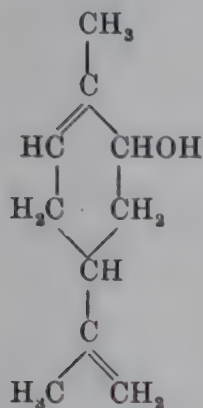
^{||} Compare Wallach and Haworth, *Annalen*, 1912, 389, 193.



The *d*-dihydrosylveterpineol, b.p. 206–209°, d^{20}_D 0.9100, n^{20}_D 1.4663, $[\alpha]_D + 1.96^\circ$ (in methyl alcohol), synthesised in this manner, although structurally identical with that prepared from sylveterpineol, differs stereochemically, since it owes its optical activity to the carbon atom (1) (marked with a cross in the formula), and which is present in the active methylcyclohexanone from which it was obtained. This stereochemical difference was confirmed by the preparation of the *phenylurethane*, m.p. 82–83°, and by the fact that on oxidation it gave an active *d*-1-methylcyclohexan-3-one ($[\alpha]_D + 8.8^\circ$). The second asymmetric carbon atom (at 3) introduced during the synthesis is assumed to be racemic.

CARVEOL

($\Delta^{6:8(9)}$ -p-Menthadien-2-ol or
1-Methyl-4-isopropenyl- Δ^6 -cyclohexen-2-ol)



The occurrence in nature of this interesting alcohol, C₁₀H₁₆O, was first recorded by Blumann and Zeitschel,* who found it to occur in small quantity in oil of caraway (from the fruits of *Carum carui* L.).

It was apparently first prepared in an impure state by Genvresse† by the action of oxides of nitrogen on limonene, but it was obtained pure by Blumann and Zeitschel, who, as mentioned already (p. 154), isolated it as a product of the autoxidation of *d*-limonene.

The alcohol, so obtained, is optically inactive and can be purified most conveniently through its crystalline *phenylurethane*, m.p. 94–95°, from which it can be regenerated by hydrolysis with alkali. Carveol is an oil, b.p. 226–227°/757 mm., 108–110°/11 mm., d^{15}_D 0.9578, n^{15}_D 1.4961. Its constitution is proved by the fact that on oxidation with chromic acid it is converted into carvone. In addition to yielding a crystalline phenylurethane, carveol gives also a crystalline *hydrogen phthalate*, m.p. 136–137°, but since carveol may exist in four optically active and two racemic forms, these derivatives may not be stereochemical individuals.

Although Ponndorf‡ obtained an optically active product by

* *Ber.* 1914, **47**, 2628.

† *Compt. rend.* 1901, **132**, 414.

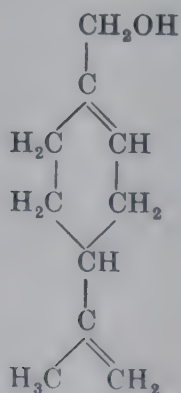
‡ *Z. angew. Chem.* 1926, **39**, 138.

the reduction of *d*-carvone with aluminium isopropoxide, it was not until 1934 that the *cis*- and *trans*-forms of both *d*- and *l*-carveol were separated, *via* their 3:5-dinitrobenzoates, by Johnston and Read.* *d*-*trans*-Carveol has b.p. 102°/10 mm., $d_4^{25^\circ}$ 0.9484, $n_D^{25^\circ}$ 1.4942, $[\alpha]_D^{25^\circ} + 213^\circ$, and gives a *p*-nitrobenzoate, m.p. 77°, and a 3:5-dinitrobenzoate, m.p. 111.5°. *d*-*cis*-Carveol has m.p. 24–25°, b.p. 101°/10 mm., $d_4^{25^\circ}$ 0.9521, $n_D^{25^\circ}$ 1.4959, $[\alpha]_D^{25^\circ} + 23.9^\circ$; the *p*-nitrobenzoate has m.p. 26.5–28°, and the 3:5-dinitrobenzoate, m.p. 92.5°. The configurations are assigned on the basis of the Auwers-Skita rule. The *cis*- and *trans*-forms of *l*-carveol, and their derivatives, have the same physical constants as those of the *d*-isomers, except of course for the specific rotations, which are opposite in sign. *dl*-*trans*-Carveol has b.p. 108°/16 mm., $d_4^{18^\circ}$ 0.9510, $n_D^{19^\circ}$ 1.4956 (*p*-nitrobenzoate, m.p. 101°; 3:5-dinitrobenzoate, m.p. 119°), whilst *dl*-*cis*-carveol has b.p. 108°/16 mm., $n_D^{19^\circ}$ 1.4972 (*p*-nitrobenzoate, m.p. 94°; 3:5-dinitrobenzoate, m.p. 91.5°).

On treatment with bromine carveol gives only liquid products, whilst, when warmed with dilute sulphuric acid, it yields *p*-cymene. If, however, it is shaken in the cold with a 5 per cent. solution of this acid, a *glycol*, m.p. 132–133°, is obtained. The constitution of this substance has not been determined.

PERILLYL ALCOHOL

(4-isoPropenyl- Δ^1 -cyclohexenecarbinol)



* *J.C.S.* 1934, p. 233.

In 1904 Schimmel and Co.* showed that in ginger-grass oil (from *Andropogon Schoenanthus* L.) there occurred, associated with geraniol, an alcohol of the formula $C_{10}H_{16}O$, which from its general properties appeared to be a dihydrocuminol. Subsequently, the same alcohol was separated by Elze from oil of bergamot,[†] oil of savin[‡] and spearmint oil,[§] and by Miller^{||} from the oil of *Monarda fistulosa* L.

The separation of the alcohol from geraniol was found to be a matter of some difficulty, since it involved the removal of the latter by treatment with formic acid, but ultimately an alcohol with the following constants was obtained, the rotatory power showing considerable variations with different samples of the oil: b.p. 226–228°, d^{15}_D 0.9510, n^{20}_D 1.4963, $[\alpha]_D - 13.18^\circ$; b.p. 228–229°, d^{15}_D 0.9536, n^{20}_D 1.4876, $[\alpha]_D + 12.5^\circ$. The alcohol was characterised very readily by the preparation of the crystalline *naphthylurethane*, m.p. 146–147°, and by oxidation with chromic acid to an *aldehyde* (*semicarbazone*, m.p. 198–199°), from which an acid, $C_{10}H_{14}O_2$, m.p. 130–131°, was prepared. The constitution of the alcohol remained undetermined until 1911, when Semmler and Zaar,[¶] during an investigation of perillaldehyde (p. 311), observed that it resembled very closely in its properties the aldehyde which had been obtained by the oxidation of the alcohol present in ginger-grass oil.

The alcohol was therefore re-examined by these authors, who found it to be identical with *l-perillyl alcohol* prepared by the reduction of *l-perillaldehyde*, although the physical properties are not in close accord, due doubtless to the difficulty in purifying the natural alcohol:

Alcohol from ginger-grass oil, b.p. 107–110°/12.5 mm., d^{20}_D 0.946, n^{20}_D 1.4968, $[\alpha]_D - 7^\circ$.

Alcohol from perillaldehyde, b.p. 119–121°/11 mm., d^{20}_D 0.9640, n^{20}_D 1.4996, $[\alpha]_D - 68.5^\circ$.

The constitution of the alcohol was, however, definitely established by its conversion into *l-limonene* by the reactions given in detail on p. 311 and by its oxidation to *l-perillaldehyde*.

* *Schimmel's Report*, 1904, April, p. 57; Oct. p. 44; 1905, April, p. 41; compare Wahlbaum and Hüthig, *J. pr. Chem.* 1905 [ii], **71**, 464.

† *Chem.-Ztg.* 1910, **34**, 538.

‡ *Ibid.* p. 1175.

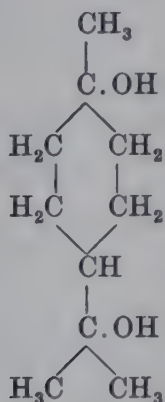
§ *Ber.* 1911, **44**, 52, 460.

¶ *Ibid.* p. 767.

|| *Circ. Univ. of Wisconsin*, 1918, No. 4.

1:8-TERPIN

(*p*-Menthane-1:8-diol or
1-Methyl-4-isopropylcyclohexane-1:8-diol)



Although the presence of 1:8-terpin, $\text{C}_{10}\text{H}_{20}\text{O}_2$, has been reported in essential oils, it is extremely unlikely that it occurs in nature and its presence is probably due to secondary reactions. It is known in both *cis*- and *trans*-modifications, whilst the former is obtained most readily in the hydrated form, *cis*-terpin hydrate.

It was observed many years ago that oil of turpentine on keeping deposited a crystalline solid, but this may have consisted of either *sobrerol* or *terpin hydrate*; it is, therefore, as a rule difficult in the earlier literature to be quite certain which of these two substances is referred to. The first mention is due to Buchner,* whilst Voget† described a method for its preparation from turpentine. In two very interesting papers Wiggers‡ described his experiments on *cis*-terpin hydrate, which he prepared from oil of turpentine; he determined correctly its empirical formula and showed that it lost water when heated at its melting-point. He found, further, that it gave a chloride when treated with hydrochloric acid. In the years following, frequent mention is made of this substance, but the next real advance in our knowledge of its chemistry was due to Oppenheim.§ He showed by the preparation of a *diacetyl* derivative that it contained two hydroxyl groups, and he would appear to

* *Repertorium*, 1820, 9, 276; 12, 419.

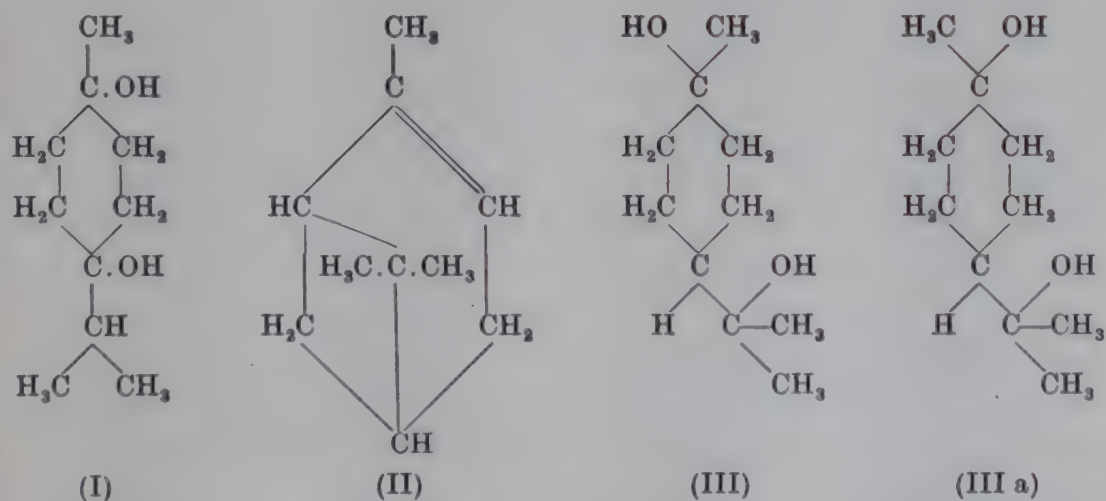
Brandes, *Arch. des Apothekvereins d. Pharm.* 1827, 23, 195.

‡ *Annalen*, 1840, 33, 358; 1846, 57, 247.

§ *Bull. Soc. chim.* 1862, 3, 84; *Compt. rend.* 1863, 57, 399; *Annalen*, 1864, 129, 149.

have been the first to recognise its relationship to cymene, into which he converted it by treating with aniline the product obtained on bromination. In 1876 Hempel* oxidised terpin hydrate with nitric acid and obtained toluic, terephthalic and terebic acids; whilst with chromic acid he separated what was evidently terpenylic acid. Two years later Tilden commenced his important investigations on the chemistry of terpin, which have been described already (p. 256). He did much to establish the relationship of terpin hydrate to terpineol. By 1880 it was recognised that terpin was a glycol, $C_{10}H_{20}O_2$, which could be prepared by the addition of two moles of water to the hydrocarbon, pinene, $C_{10}H_{16}$, and which on dehydration gave a mixture of an alcohol, $C_{10}H_{18}O$, and a hydrocarbon, $C_{10}H_{16}$, and that it could be converted into cymene. The two hydroxy groups were apparently tertiary, since the glycol did not give on oxidation either a ketone or an aldehyde.

Following the classical investigations of Wallach which are discussed on p. 257, the formula (I) was suggested by Brühl† in 1888, and it was subsequently modified to (III) by Wagner‡ in order to explain the formation of the glycol by the hydration of pinene (II).



The evidence on which the formula for α -terpineol is based has been discussed on p. 259, and since this alcohol can both be prepared from and converted into terpin, there can be no doubt

* *Annalen*, 1876, **180**, 71.

† *Ibid.* 1894, **27**, 1653.

‡ *Ber.* 1888, **21**, 462.

that formula (III) correctly represents the constitution of the glycol.

cis-Terpin was indirectly synthesised by W. H. Perkin, jun., by the hydration of synthetic α -terpineol, and subsequently, in collaboration with Kay,* he observed that, if ethyl cyclohexan-4-one carboxylate was treated with an excess of methyl magnesium iodide, *cis*-terpin hydrate was obtained, both the carboxy and carbonyl groups reacting with the Grignard reagent.

By the application of stereochemical considerations, Baeyer† recognised that terpin should exist in *cis*- and *trans*-modifications, and he was able to show that whereas *cis*-dipentene dihydrochloride gave on treatment with silver acetate *cis*-terpin hydrate, m.p. 116–117°, from the *trans*-dihydrochloride a new terpin, *trans*-terpin, m.p. 158–159°, was formed. These two terpins are the isomerides represented by formulae (III) and (III a).

cis-Terpin crystallises from water as a hydrate in rhombic pyramids which melt at 116–117° with loss of water and formation of *cis*-terpin, m.p. 104–105°. The anhydrous glycol on exposure to the air rapidly absorbs water with re-formation of the hydrate. *trans*-Terpin crystallises in monoclinic prisms, m.p. 158–159°, and does not form a hydrate.

Although *cis*-terpin (hydrate) was obtained originally by the action of dilute nitric acid on an alcoholic solution of turpentine, it is more convenient to use sulphuric acid (25 per cent.). The hydration of pinene can also be effected readily by other acids such as benzene sulphonic acid, benzoic acid, etc., for details of which reference should be made to the patent literature. A mixture of the two terpins, together with α -terpineol and other substances, is obtained by the action of dilute alkali (2 per cent.) at 50° on *trans*-dipentene dihydrochloride, but from *cis*-dihydrochloride only *cis*-terpin is formed.‡ Terpin can also be prepared by the cyclisation of linalool, geraniol,§ and nerol.|| The hydration of α -terpineol gives only the *cis*-isomeride, but from γ -terpineol both the *cis*- and *trans*-forms are obtained (compare p. 273). *cis*-Terpin is formed also by the hydration of

* J.C.S. 1907, 91, 372.

† Ber. 1893, 26, 2861.

‡ Wallach, *Annalen*, 1906, 350, 154.

§ Tiemann and Semmler, Ber. 1895, 28, 2137.

|| Zeitschel, *ibid.* 1906, 39, 1791.

the dicyclic substances dihydroverbenene* and methyl nopinol† with dilute sulphuric acid. For the preparation of *trans*-terpin free from *cis*-terpin the only method available is that used originally by Baeyer.

Very little difference is shown by the two isomerides in their general properties, and, unless special mention is made, the reactions referred to below may be regarded as applying to both.

On reduction with hydriodic acid and red phosphorus terpin yields *p*-menthane.‡ If terpin is passed over nickel in a current of hydrogen at 350–360° *p*-cymene is formed,§ but with a copper catalyst at 300° dipentene can be obtained.||

Terpin is not readily attacked by oxidising agents; it does not react with potassium permanganate at the ordinary temperature, but, when warmed with this reagent, it undergoes complete degradation to oxalic and acetic acids.¶ With chromic acid in acetic acid solution homoterpenyl methyl ketone is obtained, oxidation being evidently preceded by conversion into α -terpineol.

At the ordinary temperature bromine does not act upon terpin, but on warming indefinite substitution products are formed.** By the action of the halogen acids the dipentene dihalogenides are obtained, and although from *cis*-terpin a mixture of the *cis*- and *trans*-isomerides is formed, *trans*-terpin gives only the *trans*-derivative. As mentioned on p. 184 the action of dehydrating results in the formation of "terpineol", together with a mixture of hydrocarbons in which dipentene predominates. From *cis*-terpin some cineole is also formed,†† but this, according to Baeyer,** is not the case with *trans*-terpin, which gives only α -terpineol.

A number of esters of *cis*-terpin have been described, the *diacetate* boiling at 140–141°/10 mm. and the *diformate* at 176–177°/40 mm.

* Blumann and Zeitschel, *Ber.* 1921, **54**, 887. † Lipp, *ibid.* 1923, **56**, 2105.

‡ Schtschubkaraev, *J. Russ. Phys. Chem. Soc.* 1890, **22**, 297; Konowalov, *ibid.* 1906, **38**, 449. § Sabatier and Gaudion, *Compt. rend.* 1919, **168**, 671.

|| Neave, *J.C.S.* 1912, **101**, 514.

¶ Tiemann and Schmidt, *Ber.* 1895, **28**, 1782.

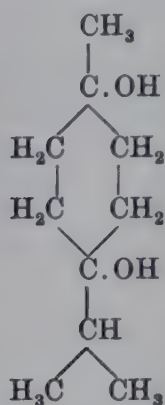
** Wallach, *Annalen*, 1885, **230**, 248; Barbier, *Bull. Soc. chim.* 1872 [ii], **17**, 17.

†† Wallach, *Annalen*, 1887, **239**, 18; 1889, **252**, 133; compare Mosher, quoted by Stevens and Greenwood, *J. Amer. C.S.* 1943, **65**, 2154, footnote 11.

** *Ber.* 1893, **26**, 2865.

TERPINENE-TERPIN (1:4-TERPIN)

(*p*-Menthane-1:4-diol or
1-Methyl-4-isopropylcyclohexane-1:4-diol)



Terpinene-terpin (I) does not occur in nature. It was prepared by Wallach* by the action of very dilute alkali (2 per cent.) on *terpinene dihydrochloride* (II). The yield of the terpin, when prepared by this method, is however extremely small and it was subsequently† found to be more readily obtained by the hydration of *sabinene* (III), α -*thujene* (IV) or *terpinen-4-ol* (V) with dilute sulphuric acid. It can be prepared also by the action of methyl magnesium iodide on *sabina ketone* (V), the resulting alcohol (VII) yielding the terpin on treatment with sulphuric acid.‡

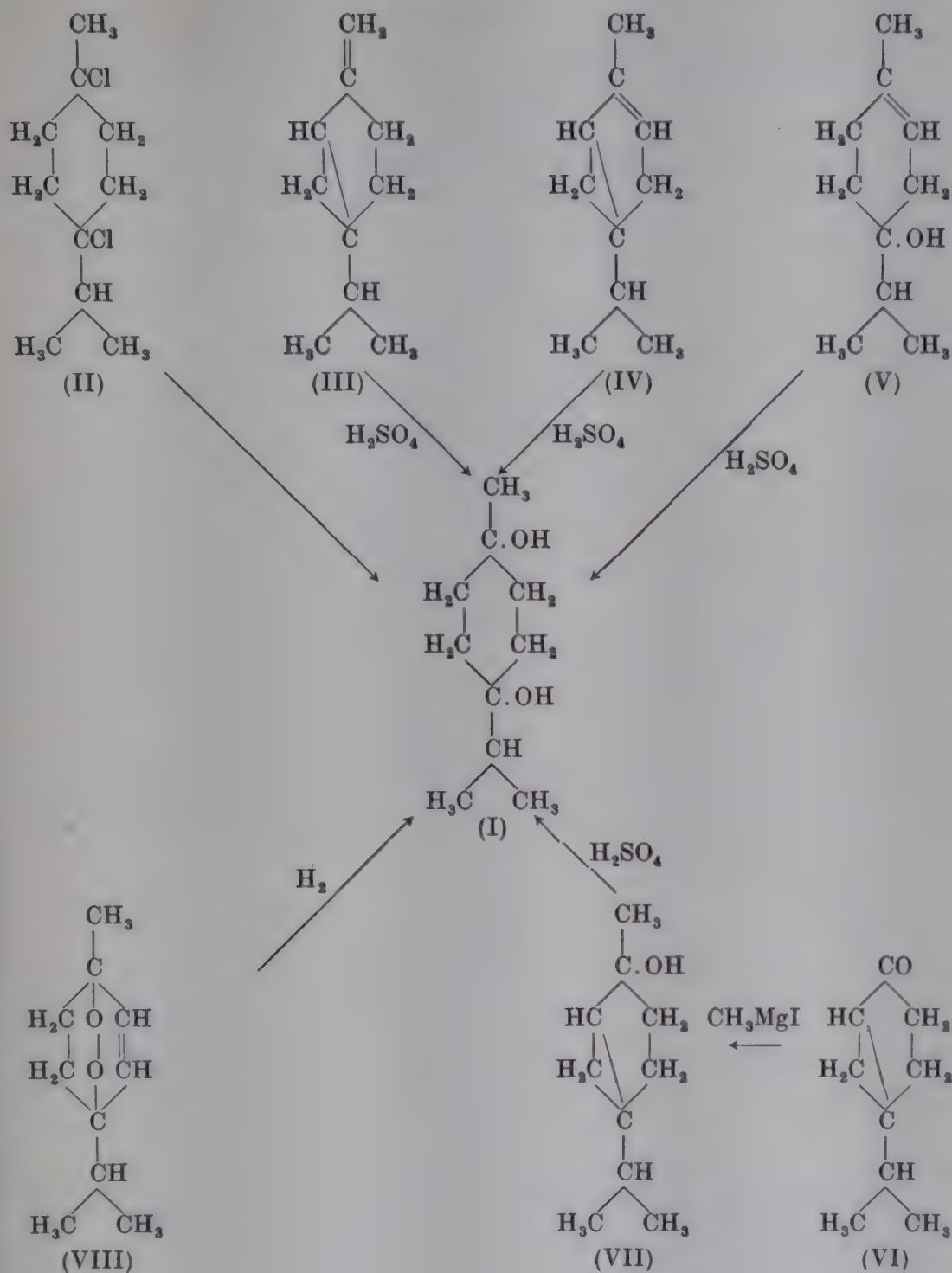
When prepared by any of these methods terpin crystallises in leaflets, m.p. 137–138°, and it is probably the *trans*-modification of the alcohol, since in 1912 Wallach§ showed that when *ascaridole* (VIII) was hydrogenated in the presence of a palladium catalyst, an isomeric *terpin*, m.p. 116–117°, was obtained, which from its method of preparation would appear to have the *cis*-configuration. No direct chemical evidence of the correct stereochemical formulae of these isomerides is, however, available. On dehydration they both yield with equal facility 1:4-cineole (p. 433) and the unsaturated alcohols, *terpinen-4-ol* and *terpinen-1-ol*. With the halogen acids, both terpins yield the corresponding terpinene dihalogenides.

* *Annalen*, 1906, **350**, 157.

‡ Wallach, *ibid.* 1907, **357**, 64.

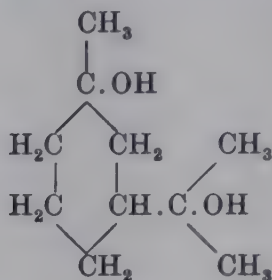
† Wallach, *ibid.* 1907, **356**, 200.

§ *Ibid.* 1912, **392**, 59.

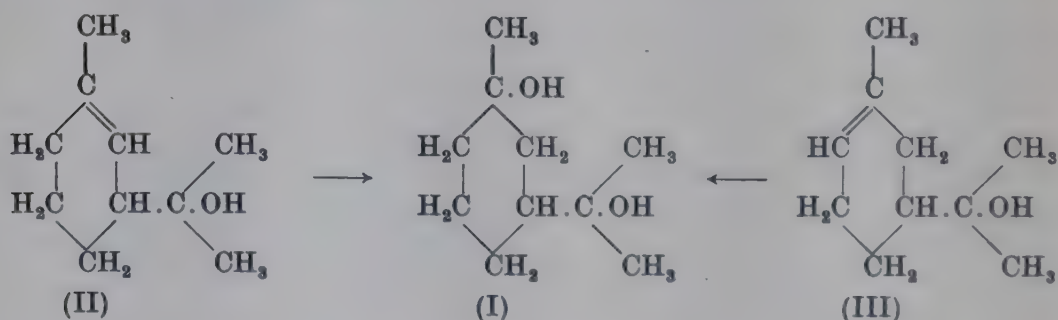


SYLVETERPIN (CARVETERPIN)

(*m*-Menthane-1:8-diol or
1-Methyl-3-isopropylcyclohexane-1:8-diol)



The racemic *trans*-terpin, C₁₀H₂₀O₂, of the *m*-cymene series, *carveterpin* (I), m.p. 126–127°, was first described by Baeyer,* who prepared it from carvestrene dihydrobromide by the action of silver acetate and then of alcoholic potassium hydroxide, a method adopted later by Perkin and Tattersall,[†] who used, however, the synthetic dihydrobromide (compare p. 219). The *cis*-modification, m.p. 94°, was prepared by these authors by the hydration of *dihydrocarvestrenol* (II) with dilute sulphuric acid, and also by Fisher and Perkin[‡] from *dihydroisocarvestrenol* in a similar manner.



The corresponding optically active *d*-*trans*-sylveterpin, m.p. 137–138°, was prepared by Wallach[§] by the action of dilute aqueous potassium hydroxide on *d*-sylvestrene dihydrochloride. A subsequent investigation of this reaction by Haworth, Perkin and Wallach^{||} showed that at the same time the *d*-*cis*-modification, m.p. 70–75°, was also formed. The latter is very much more soluble and is obtained from the final mother liquors when the

* *Ber.* 1894, 27, 3490.

‡ *Ibid.* 1908, 93, 1889.

|| *J.C.S.* 1913, 103, 1233.

† *J.C.S.* 1907, 91, 480.

§ *Annalen*, 1907, 357, 73.

benzene solution of the two terpins is fractionally precipitated with light petroleum. Both sylveterpins are also formed by the hydration of *d-sylveterpineol* (p. 294) with dilute sulphuric acid.

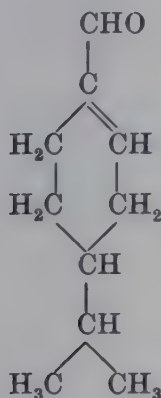
d-cis-Sylveterpin or β -*sylveterpin* has $[\alpha]_D + 20.93^\circ$ in chloroform and $[\alpha]_D + 18.48^\circ$ in methyl alcohol, whilst *d-trans-sylveterpin* or α -*sylveterpin* has $[\alpha]_D + 27.74^\circ$ in chloroform. The two isomerides resemble closely in their properties the terpins of the *p*-cymene series, except that they are very much more soluble in water and the *cis*-modification does not form a hydrate. On treatment with hydrogen bromide they both yield a mixture of the *cis*- and *trans*-sylvestrene dihydrobromides in which the *trans*-form largely predominates. (The two carveterpins behave similarly.) When *d-trans-sylveterpin* is oxidised with potassium permanganate in aqueous solution one of the products of the oxidation is acetone.

CHAPTER III

ALDEHYDES

PELLANDRAL

(4-isoPropyl- Δ^1 -cyclohexenaldehyde)



In 1909 Schimmel and Co.* separated from water fennel oil (*Phellandrium aquaticum* L.) an aldehyde, C₁₀H₁₆O, to which the name *phellandral* was given. Subsequently Penfold† showed that phellandral was present in the oils from *Eucalyptus hemiphloia*, *E. polybractea*, and *E. Bakeri* Maiden.

l-Phellandral can be most readily isolated and purified by taking advantage of the fact that it yields a sparingly soluble crystalline compound with sodium hydrogen sulphite, from which it can be regenerated by treatment with alkali. When purified in this manner, the aldehyde from *P. aquaticum* was found to have the following constants: b.p. 89°/5 mm., d^{15}_4 0.9445, n^{20}_D 1.4916, $\alpha_D - 36.3^\circ$. Very similar values were obtained by Penfold for the aldehyde prepared by him from *E. hemiphloia* except that the rotation was considerably higher: b.p. 90°/5 mm., d^{20}_4 0.9412, n^{20}_D 1.4912, $\alpha_D - 130.85^\circ$. The purest specimen of *l*-phellandral so far obtained is that isolated from *E. cneorifolia* by Cook and Macbeth,‡ who obtained a product b.p. 75°/1.5 mm.,

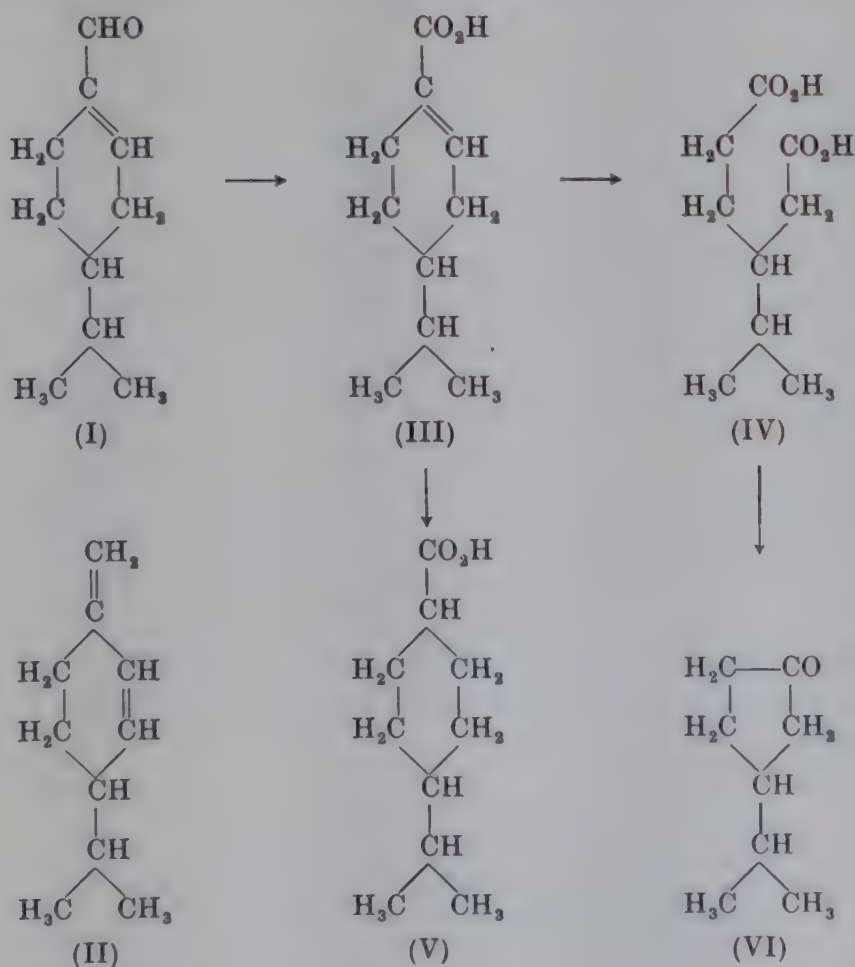
* *Schimmel's Report*, 1904, Oct. p. 88.

† *J.C.S.* 1922, 121, 266; *J. Proc. Roy. Soc. New South Wales*, 1927, 61, 185.

‡ *J.C.S.* 1938, p. 1408.

n_D^{20} 1.4897, α_D^{20} -151.3° , by regeneration from the *semicarbazone*, m.p. $204-205^\circ$. Other derivatives suitable for characterisation are the *oxime*, m.p. 87° , and the *phenylhydrazone*, m.p. $122-123^\circ$ (see also the *d*-form below).

Although Schimmel and Co. reported a laevorotation for the phellandral isolated by them from water fennel oil, Berry, Macbeth and Swanson* have obtained from this source a *d*-phellandral, $\alpha_D +116.2^\circ$ (*semicarbazone*, m.p. 200° ; *p*-nitro-*phenylhydrazone*, m.p. $174-175^\circ$; 2:4-dinitro-*phenylhydrazone*, m.p. 204°). A biogenetic relationship between phellandral (I) and β -phellandrene (II) is implied by the observations that the *d*-aldehyde is usually accompanied by the *d*-hydrocarbon, and the *l*-aldehyde occurs with the *l*-hydrocarbon; it has already been mentioned (p. 207) that Wallach prepared an aldehyde, probably identical with phellandral, by the oxidation of β -phellandrene.



* *J.C.S.* 1937, p. 1448.

The constitution of phellandral is probably represented by (I), since on exposure to the air or by treatment with moist silver oxide both the *d*- and the *l*-forms are oxidised to *phellandric acid* (III), $C_{10}H_{16}O_2$, m.p. 144–145°, $[\alpha]_D \pm 113^\circ$. On further oxidation with potassium permanganate it gives a dibasic acid, $C_9H_{16}O_4$, m.p. 70–72°, which is possible only if the parent acid is an unsaturated cyclic compound with the ethylenic linkage in the $\alpha\beta$ -position to the carboxyl group. Phellandric acid is therefore 4-isopropyl- Δ^1 -cyclohexene-1-carboxylic acid (III) and the dibasic acid β -isopropyladipic acid (IV). Both the *d*- and the *l*-forms of the latter acid have been obtained by Burger and Macbeth,* who give m.p. 73–73.5°, $[\alpha]_D \pm 0^\circ$ (1-p-bromophenacyl ester, m.p. 63–64°, $[\alpha]_D^{25^\circ} - 7.41^\circ$ in alcohol). This curious instance of enantiomorphs showing an immeasurably small rotation had already been noted by Braun and Werner,† who also resolved the *dl*-acid with strychnine, though for the *d*-form they gave m.p. 66° and obtained the *l*-form only in an impure state. The carbon skeleton of *d*- and *l*-phellandric acids has been established by their hydrogenation‡ to a dihydro-derivative which can be isolated in *cis*- and *trans*-modifications, both of which are optically inactive and are identical with the *cis*- and *trans*-hexahydrocuminic acids (V). *dl*-Phellandric acid, m.p. 143–144°, has been synthesised by the same authors from α -bromohexahydrocuminic acid, and it only remains to resolve this product for comparison with the optically active forms derived from the natural aldehydes.

When the calcium salt of the dibasic acid (IV) is distilled, it yields a ketone, b.p. 190–193°, $[\alpha]_D^{20^\circ} + 190^\circ$ or -191.3° (*semicarbazone*, m.p. 187°), which is probably 3-isopropylcyclopentan-1-one (VI).§

Hydrogenation of *l*-phellandral|| in the presence of palladium gives *dihydrophellandral*, b.p. 61.5°/1.5 mm., $n_D^{20^\circ} 1.4572$, $\alpha_D \pm 0^\circ$ (*semicarbazone*, m.p. 172–173°).

* *J.C.S.* 1946, p. 145.

† *Ber.* 1929, 62, 1054.

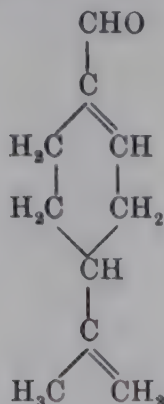
‡ Cooke, Macbeth and Swanson, *J.C.S.* 1940, p. 808.

§ Burger and Macbeth, *loc. cit.*

|| Cooke and Macbeth, *J.C.S.* 1938, p. 1408.

PERILLALDEHYDE

(4-isoPropenyl- Δ^1 -cyclohexenaldehyde)



l-Perillaldehyde, $C_{10}H_{14}O$, occurs in the oils obtained from *Perilla nankinensis* Decne,* and in that from the ripe fruits of *Siler trilobum* Scop.,† whilst *d*-perillaldehyde has been obtained from the oil of “false camphor wood” derived from *Hernandia peltata*.‡

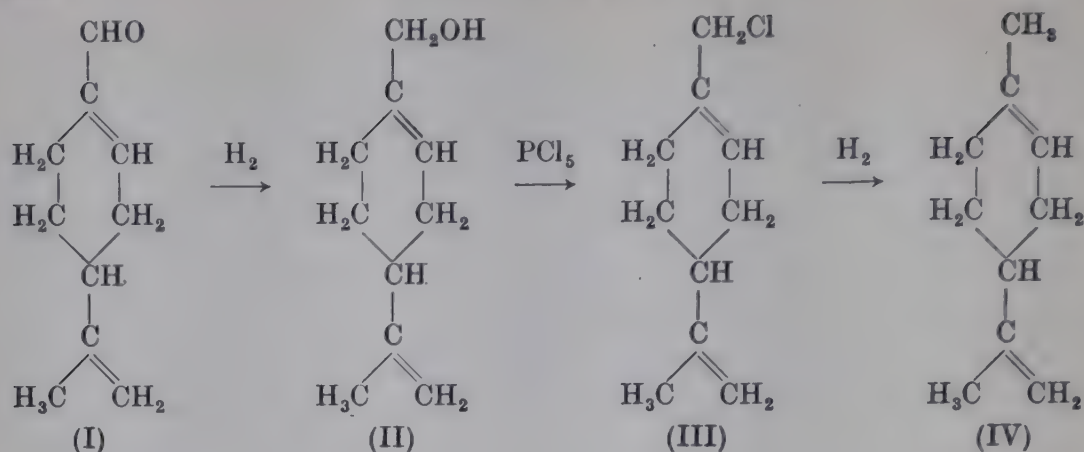
The constitution of the aldehyde was determined by Semmler and Zaar.§ After purification through its crystalline compound with sodium hydrogen sulphite, it was obtained as an oil, b.p. $104\text{--}105^\circ/10\text{ mm.}$, d^{18}_D 0.9617, n_D 1.5074, $[\alpha]_D - 146^\circ$; the dextro form was not of equal purity, since $[\alpha]_D + 135.6^\circ$ was observed. The high value for the molecular refraction (obs. 46.4, calc. 45.52) indicated the presence of two ethylenic linkages, thus suggesting that perillaldehyde was a dihydrocuminaldehyde. This was confirmed by a study of its reactions.

On reduction with zinc in the presence of acetic acid, the acetate of an alcohol, b.p. $123\text{--}126^\circ/13\text{ mm.}$, d^{20}_D 0.9785, n_D 1.4814, $[\alpha]_D - 48^\circ$, was obtained, which on hydrolysis gave the alcohol *l*-perillyl alcohol (II), b.p. $119\text{--}121^\circ/11\text{ mm.}$, d^{20}_D 0.9640, n_D 1.4996, $[\alpha]_D - 68.5^\circ$. When the alcohol was treated with phosphorus pentachloride *l*-perillyl chloride (III), b.p. $99\text{--}101^\circ/12\text{ mm.}$, d^{20}_D 0.9861, n_D 1.4973, $[\alpha]_D - 60^\circ$, was formed and this gave on reduction with sodium and alcohol *l*-limonene (IV). These reactions leave no doubt that *l*-perillaldehyde must be represented by formula (I).

* Schimmel's Report, 1910, Oct. p. 146; Furuwaka and Tomizawa, *J. Chem. Ind. Tokyo*, 1920, 23, 342. † Rutovski and Gusseva, *Riechstoffindustrie*, 1927, p. 230.

‡ Semmler and Zaar, *Ber.* 1911, 44, 815.

§ *Ibid.* p. 52.

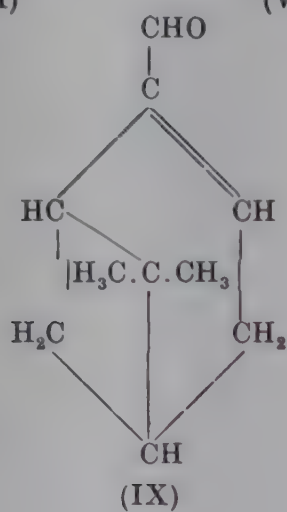
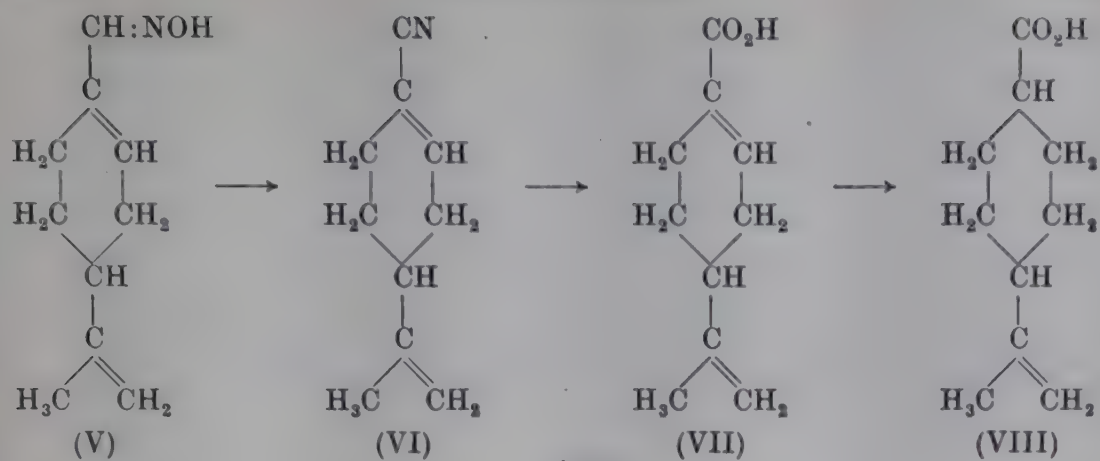


Perillaldehyde can be characterised by the preparation of the *semicarbazone*, m.p. 199–200°, the *oxime*, m.p. 102°, and the *phenylhydrazone*, m.p. 107.5°. According to Furuwaka and Tomizawa, the oxime can be obtained in two forms, the α -*anti*-oxime, m.p. 102°, and the β -*syn*-oxime, m.p. 129°; the former is stated to have a very sweet taste, the latter being tasteless. On exposure to the air the aldehyde is readily oxidised to an acid *perillic acid*, C₁₀H₁₄O₂, m.p. 132–133°, which is presumably 4-isopropenyl- Δ^1 -cyclohexene-1-carboxylic acid (VII). The same acid can be prepared from the oxime (V), which, when treated with sodium acetate in acetic acid solution, yields *perillonitrile* (VI), b.p. 116–118°/11 mm., and this on hydrolysis gives the acid (VII), the *amide* of which has m.p. 164–165°. When this acid is reduced with sodium and alcohol addition of a molecule of hydrogen takes place with the formation of an acid, C₁₀H₁₆O₂, m.p. 107–109°, which is probably 4-isopropenylcyclohexane-1-carboxylic acid (VIII).

Rutovski and Korolev* have shown that perillaldehyde will condense readily with acetaldehyde and acetone to yield *perillylideneacetaldehyde* and *perillylideneacetone*, whilst, when condensed with hippuric acid in the presence of acetic anhydride and sodium acetate, an *oxazolone* is obtained.

As has been remarked by Semmler and Zaar, it is of phytochemical interest that in “false camphor wood” oil both *d*-perillaldehyde and *myrtenal* (IX) occur, since these two aldehydes are related to one another in the same manner as dipentene is to α -pinene.

* *Trans. Sci. Chim.-Pharm. Inst. Moscow*, 1928, p. 153; compare Williams, *J. Russ. Phys. Chem. Soc.* 1929, 61, 1573.

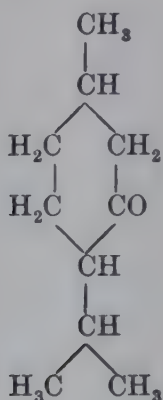


CHAPTER IV

KETONES

MENTHONE

(*p*-Menthane-3-one or 1-Methyl-4-isopropylcyclohexan-3-one)



l-Menthone, C₁₀H₁₈O, was probably first prepared in a pure state by Moriya* by the oxidation of *l*-menthol, but its occurrence in nature was not observed until about ten years later, when Andres and Andreef† separated it from Russian peppermint oil. Since menthone contains two asymmetric carbon atoms it can exist in two externally compensated and four optically active modifications, which have been designated *d*-, *l*- and *dl*-menthone and *d*-, *l*- and *dl*-isomenthone. The ketone present in peppermint oils, geranium oil (from *Pelargonium odorantissimum* Willd.)‡ and pennyroyal oils§ would appear to consist almost entirely of *l*-menthone, although Barrowcliff found that American pennyroyal oil contained a small percentage of *d*-isomenthone; whilst it is possible that *l*-isomenthone occurs in buchu leaf oil (from *Barosma betulina*).|| In neither case, however, has the occurrence of these isomerides been fully established.

* *J.C.S.* 1881, 39, 77.

† *Ber.* 1892, 25, 617.

‡ Flatau and Labbé, *Bull. Soc. chim.* 1898 [iii], 19, 788; Schimmel's Report, 1904, Apr. p. 50; compare Zeitschel and Eck, *J. pr. Chem.* 1932 [ii], 133, 365.

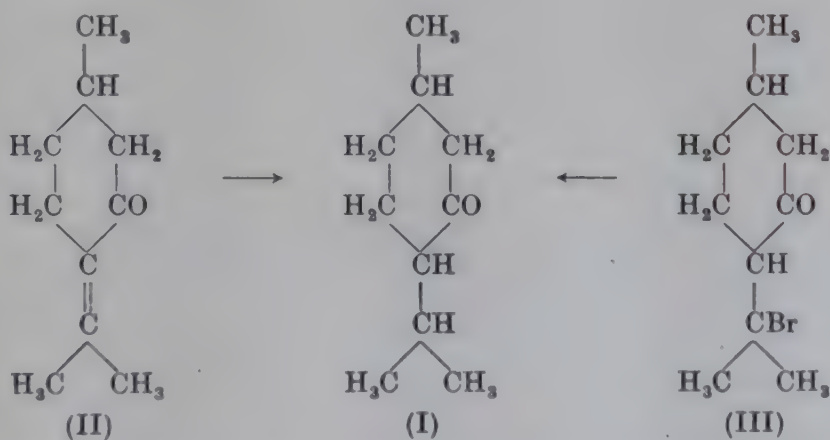
§ Tétay, *Bull. Soc. chim.* 1902 [iii], 27, 192; Barrowcliff, *J.C.S.* 1907, 91, 881.

|| Kondakov, *J. pr. Chem.* 1896 [ii], 54, 438; Kondakov and Bachtshiev, *ibid.* 1901 [ii], 63, 54.

The evidence upon which the constitution of menthol is based is discussed on p. 231 and, since menthone is the ketone corresponding to this secondary alcohol, it is clear that it must be represented by the formula given at the head of this section. This has been fully confirmed by the numerous syntheses of the ketone, some of the more important of which are described below. The methods which have been employed for the preparation and purification of the isomeric menthones have been given on pp. 234–242, where will also be found details of their physical properties and those of their more important derivatives. The absorption spectrum of menthone in the ultra-violet has been observed by Henderson, Henderson and Heilbron,* and has been shown to resemble that of acetone, the cyclic system evidently having little influence.

l-Menthone can be identified most readily by the preparation of the *oxime*, m.p. 59°, and the *semicarbazone*, m.p. 187°. *dl*-*Menthone-2:4-dinitrophenylhydrazone* has m.p. 142°.†

The first synthesis of menthone (I) was that involved in its preparation from menthol by Moriya,‡ but of greater importance was the observation of Beckmann and Pleissner§ that it could be obtained by the reduction of *d*-pulegone (II) or *d*-pulegone hydrobromide (III).



Of interest also is its formation from citronellal, to which reference is made on p. 81. Menthone has been prepared also

* *Ber.* 1914, **47**, 876; compare Purvis, *J.C.S.* 1924, **125**, 413; Lowry and Lishmund, *ibid.* 1935, pp. 709, 1313; Cooke and Macbeth, *ibid.* 1938, p. 1408; Mohler and Lohr, *Helv. Chim. Acta*, 1937, **20**, 1183.

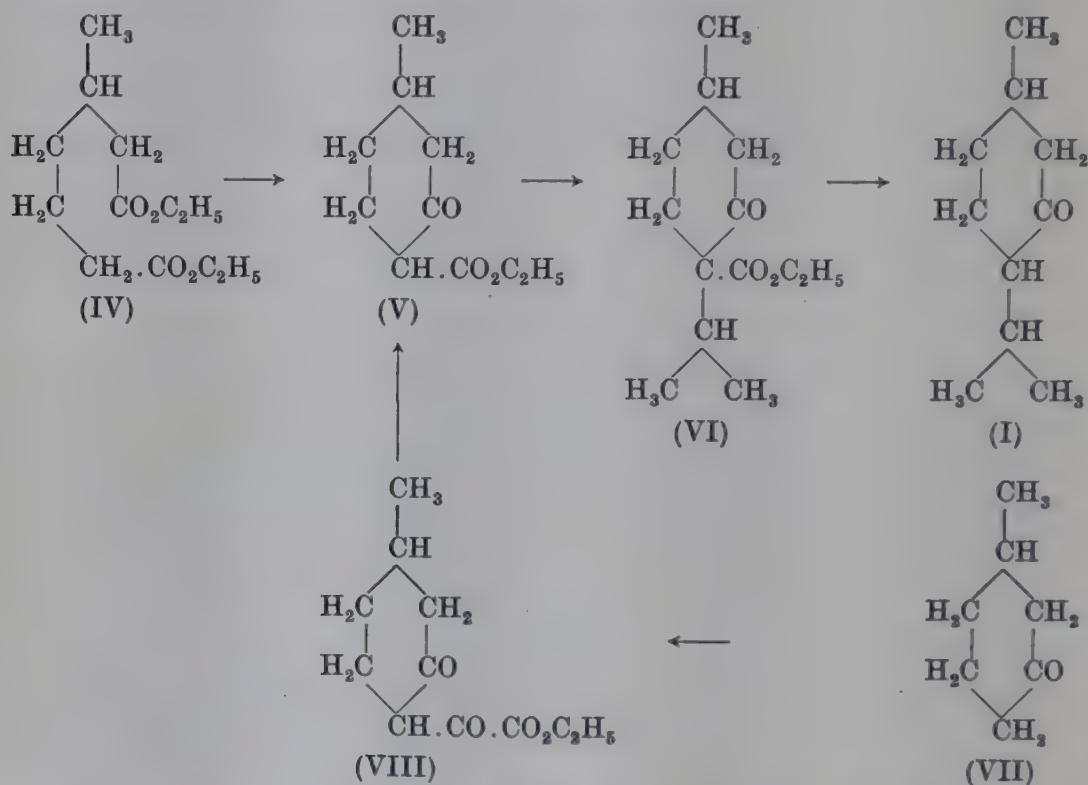
† Penfold, Ramage and Simonsen, *J.C.S.* 1939, p. 1496.

‡ *J.C.S.* 1881, **39**, 77.

§ *Annalen*, 1891, **262**, 21.

by the reduction of piperitone and other unsaturated ketones (compare p. 240).

The first rational synthesis of menthone was probably that devised by Einhorn and Klages.* When *ethyl β-methylpimelate* (IV) is treated with sodium it yields the sodium derivative of *ethyl 4-methylcyclohexan-2-one carboxylate* (V), and this gives with *isopropyl iodide* *ethyl 4-methyl-1-isopropylcyclohexan-2-one carboxylate* (VI), from which by hydrolysis and elimination of carbon dioxide menthone (I) is obtained.



A synthesis on somewhat similar lines was carried out by Kötze and Hesse,[†] who, by the condensation of *d*-3-methylcyclohexanone (VII) with ethyl oxalate, prepared the *ester* (VIII), which by the action of heat was converted into (V), from which by the method of Einhorn and Klages menthone was prepared. Since the methylcyclohexanone used by Kötze and Hesse was dextrorotatory a feebly dextrorotatory menthone was obtained.

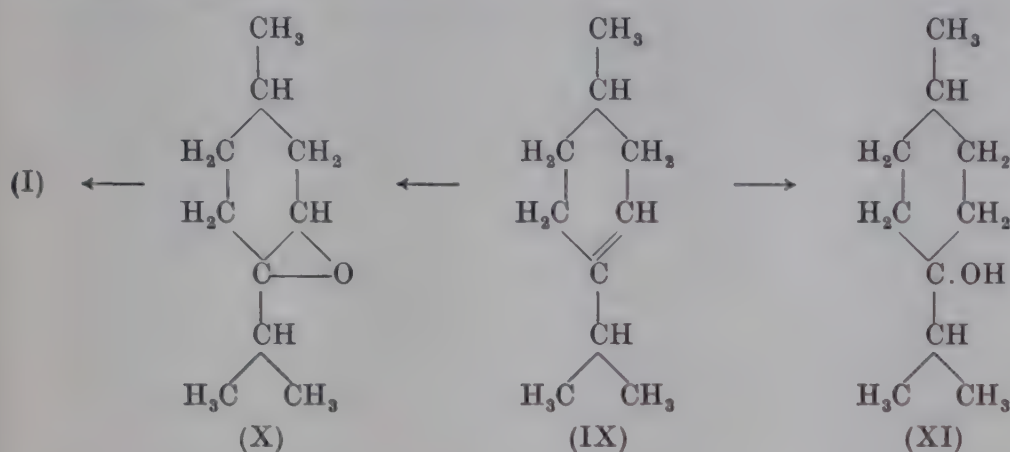
A more direct synthesis from *d*-3-methylcyclohexanone was devised by Haller,[‡] who condensed the ketone with *isopropyl iodide* in the presence of sodamide and obtained a *d*-menthone.

* Ber. 1901, 34, 3793.

† Annalen, 1905, 342, 306.

‡ Compt. rend. 1904, 138, 1139; Haller and Martine, *ibid.* 1905, 140, 130.

Kötz and Busch* described a novel synthesis in which they oxidised Δ^3 -*p*-menthene (IX) with benzoylhydroperoxide to the oxide (X) which, on digestion with an alcoholic solution of hydrogen chloride, gave menthone. It is of interest to note that hydration of the unsaturated hydrocarbon gives not menthol but the *tertiary* alcohol (XI).



Attention has been directed already to the comparative instability of *l*-menthone and to its conversion into *d*-isomenthone (p. 234). Reduction with hydriodic acid and red phosphorus yields *p*-menthane, although its formation is accompanied by some fission of the ring. With other reducing agents a mixture of the stereoisomeric menthols is obtained in excellent yield; according to Law,[†] on electrolytic reduction in sulphuric acid-alcoholic solution, the formation of menthol is accompanied by two *pinacones*, m.p. 172–173° and 148–150°, respectively, which are not identical with the pinacone described by Beckmann,[‡] which melts at 94° and is formed when menthone is reduced with sodium in ethereal solution.

Bamford and Norrish[§] have shown that the photolysis of menthone in the vapour phase gives propylene and 3-methylcyclohexanone.

The oxidation of menthone in alcoholic solution in the presence of sunlight was investigated by Ciamician and Silber,^{||} who found that *d*-2:6-dimethyl- Δ^3 -octen-8-al (XII) together with the

* *J. pr. Chem.* 1928 [ii], 119, 1.

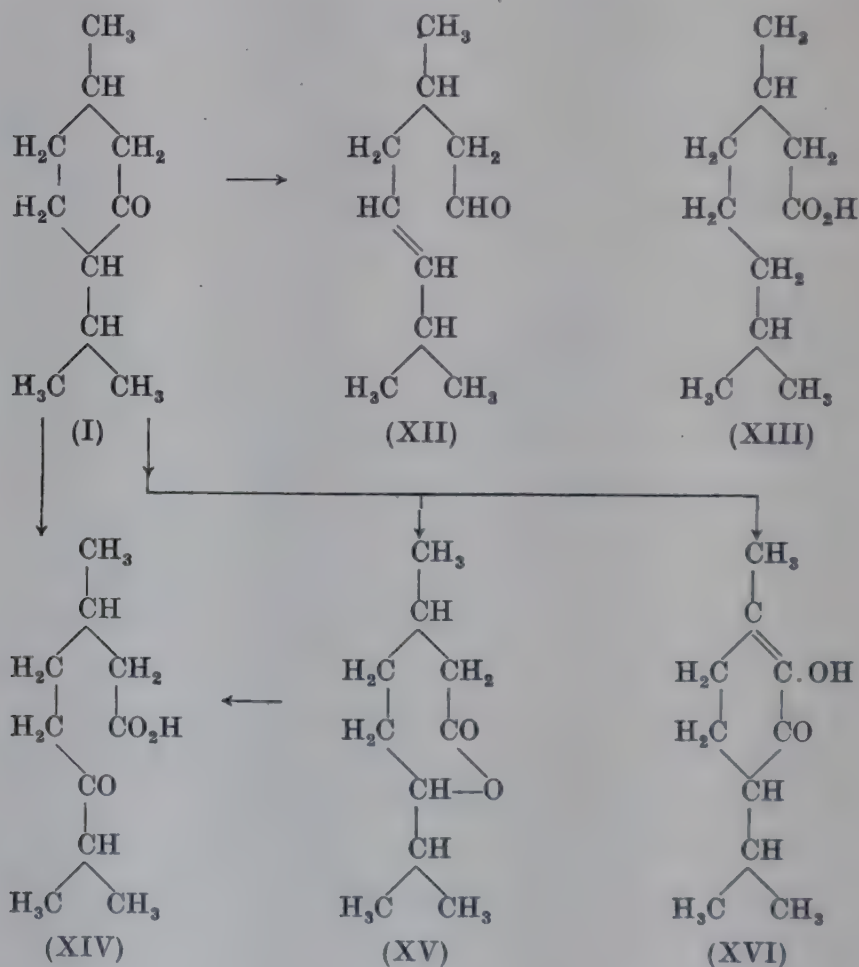
† *J.C.S.* 1912, 101, 1026; compare Schall and Kirst, *Zeit. Elektrochem.* 1924, 29, 537.

‡ *J. pr. Chem.* 1897 [ii], 55, 18.

§ *J.C.S.* 1938, p. 1521.

|| *Ber.* 1907, 40, 2419; 1909, 42, 1510.

corresponding saturated *acid* (XIII) were formed, whilst, in the presence of oxygen, the *ketonic acid* (XIV) was the main product of the reaction. This acid, *β-methyl-δ-isobutyryl-n-valeric acid*, is obtained also by the oxidation of menthone with chromic acid in acetic acid solution* or with hydrogen peroxide and vanadium pentoxide.† Caro's reagent was found by Baeyer and Villiger‡ to give the *ε-lactone* of 2:6-dimethyloctan-3-ol carboxylic acid (XV), from which, by oxidation with chromic acid, the ketonic acid (XIV) could be prepared. By the action of ferric chloride in acetic acid solution menthone is oxidised to *diosphenol* (XVI).§



With potassium permanganate as the oxidising agent, the main product has been shown to be *d-β-methyladipic acid*

* Beckmann and Mehrländer, *Annalen*, 1896, **289**, 368.

† Treibs, *Ber.* 1939, **72**, 1194.

‡ *Ibid.* 1899, **32**, 3625.

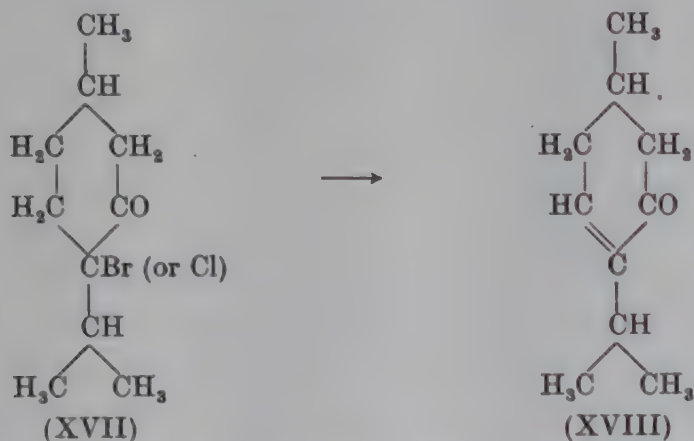
§ Asahina and Mituhori, *J. Pharm. Soc. Japan*, 1922, April, p. 1.

together with the ketonic acid (XIV), methylsuccinic acid and other acids being formed in smaller amounts.*

Dehydrogenation of menthone to thymol has been accomplished by heating the ketone with palladium[†] or with active carbon.[‡]

The products which are obtained by the halogenation of menthone show considerable variation, dependent both upon the solvent and the quantity of halogen used.

Kötz and Steinhorst[§] showed that with one molecule of bromine (or chlorine) it is possible to prepare a monohalogenated ketone, which must be 4-bromo- (or chloro-) menthone (XVII) (b.p. 120–122°/16 mm. and 115–117°/15 mm. respectively) since, on digestion with sodium acetate in acetic acid solution, Δ^4 -p-menthen-3-one (XVIII) is formed.



The chloride can also be prepared indirectly from bis-nitroso-menthone (see p. 321).

With two molecules of bromine, d-2:4-dibromomenthone (XIX) is obtained, a substance which was first prepared by Beckmann and Mehrländer.^{||} The bromide, m.p. 79–80°, $[\alpha]_D + 199.4^\circ$, is best prepared by the bromination of *l*-menthone in acetic acid solution. The action of potassium hydroxide on the dibromide was investigated by Cusmano[†] and by Wallach,^{**} who showed that it gave a mixture of two substances, m.p. 82–83° and 36–38° respectively; of these the latter was unstable and passed slowly

* Manasse and Rupe, *Ber.* 1894, **27**, 1818; Markownikov, *ibid.* 1900, **33**, 1908; *J. Russ. Phys. Chem. Soc.* 1903, **35**, 226; Speranski, *ibid.* 1901, **34**, 10.

† Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

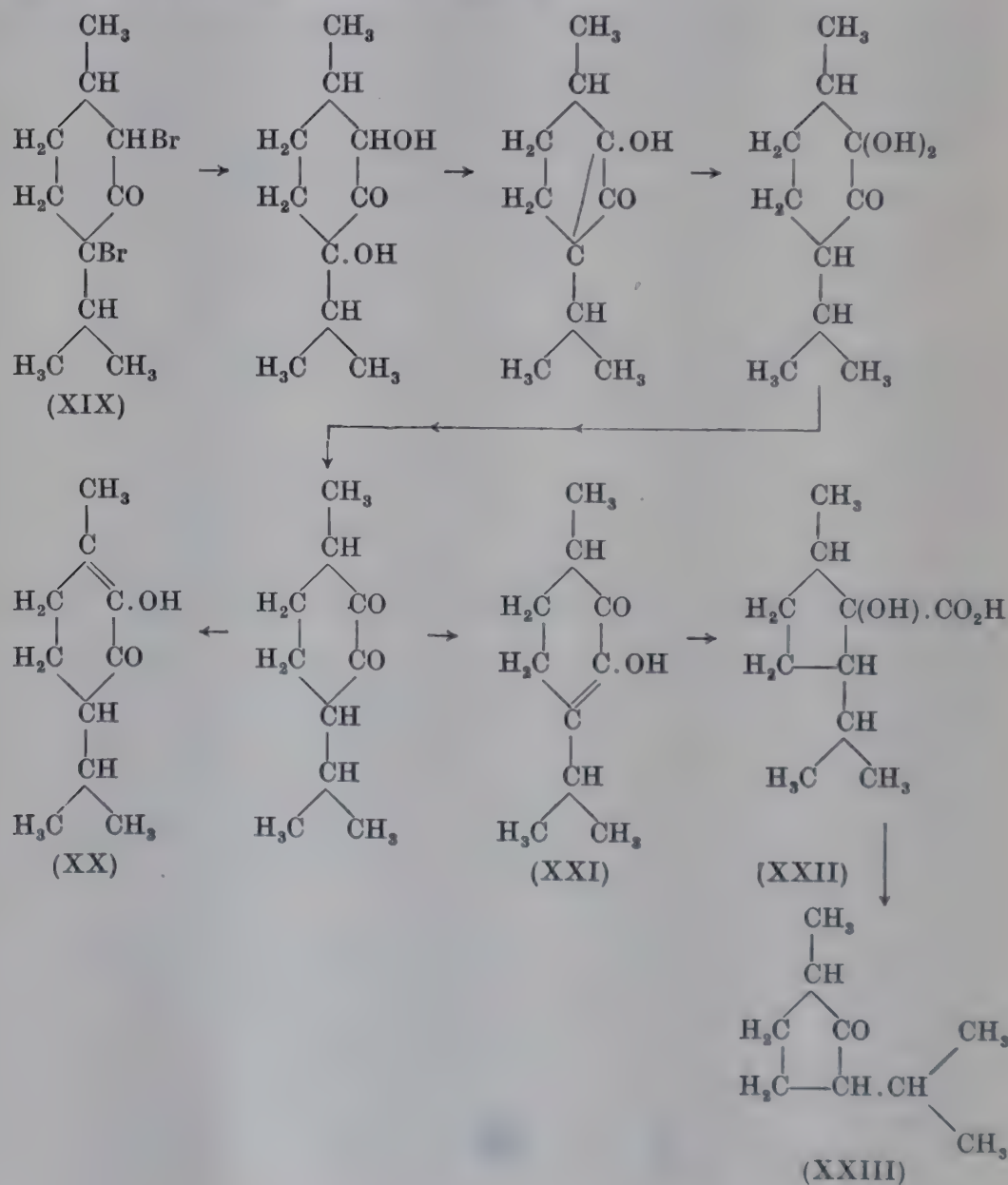
‡ Kimura, *Bull. Chem. Soc. Japan*, 1935, **10**, 330. § *Annalen*, 1911, **379**, 22.

|| *Ibid.* 1896, **289**, 376; Beckmann and Eickelberg, *Ber.* 1896, **29**, 418.

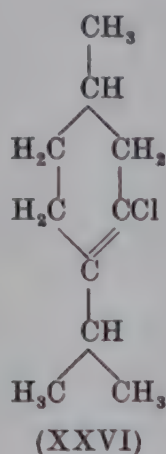
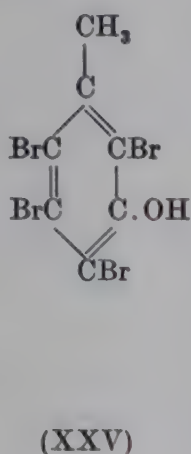
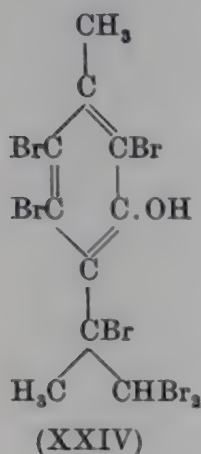
¶ *Atti R. Accad. Lincei*, 1913 [v], **22**, II, 569.

** *Annalen*, 1918, **414**, 273.

into the former. An acid, $C_{10}H_{18}O_3$, was also formed. A study of the properties of these substances has shown the former, m.p. $82-83^\circ$, to be identical with diosphenol (XX), whilst the latter, m.p. $36-38^\circ$, is probably the isomeric *hydroxy-ketone* (XXI). Since the acid, on oxidation with potassium permanganate in acid solution, gives *dihydrocamphorone* (XXIII), it is undoubtedly the *cyclopentane acid* (XXII) formed from (XXI) by a Wagner-Meerwein rearrangement. The probable mechanism involved in the formation of these substances is illustrated schematically below and it is interesting to note that dibromocarvomenthone reacts in a similar manner (see p. 331).



According to Oddo,* if the bromination is carried out in alcoholic solution, in addition to the dibromide, thymol is also formed. The conversion of menthone into halogenated phenols was found by Baeyer and Seuffert† to occur if the ketone was treated with a large excess of bromine, when *hexabromothymol* (XXIV) and *tetrabromo-m-cresol* (XXV) are formed. With phosphorus pentachloride the unsaturated chloride, *3-chloro-p-menthene* (XXVI) is obtained.‡



Menthone is not attacked by dehydrating agents in the cold, but, if warmed with phosphorus pentoxide, it yields mainly a *diterpene*, $C_{20}H_{32}$, only very small quantities of simpler hydrocarbons being formed.

When menthone is treated with nitrous acid, preferably prepared by the action of acetyl chloride on amyl nitrite,[§] it gives a crystalline *bis-nitroso-derivative* (XXVII), m.p. 112.5° , together with a small quantity of the *oxime* of β -methyl- δ -isobutyryl-*n*-valeric acid (XXVIII), m.p. 103° . On hydrolysis of bis-nitrosomenthone with hydrochloric acid a mixture of the *nitrosylic acid* (XXIX) and the *chloroketone* (XVII) is obtained.

Theoretically it should be possible to prepare an isomeric nitroso-derivative in which the nitroso-group is attached to the carbon atom (2), and, according to Oddo,^{||} it is formed by the action of nitrous acid on menthone-2-carboxylic acid, the pre-

* *Gazzetta*, 1897, 27, II, 112.

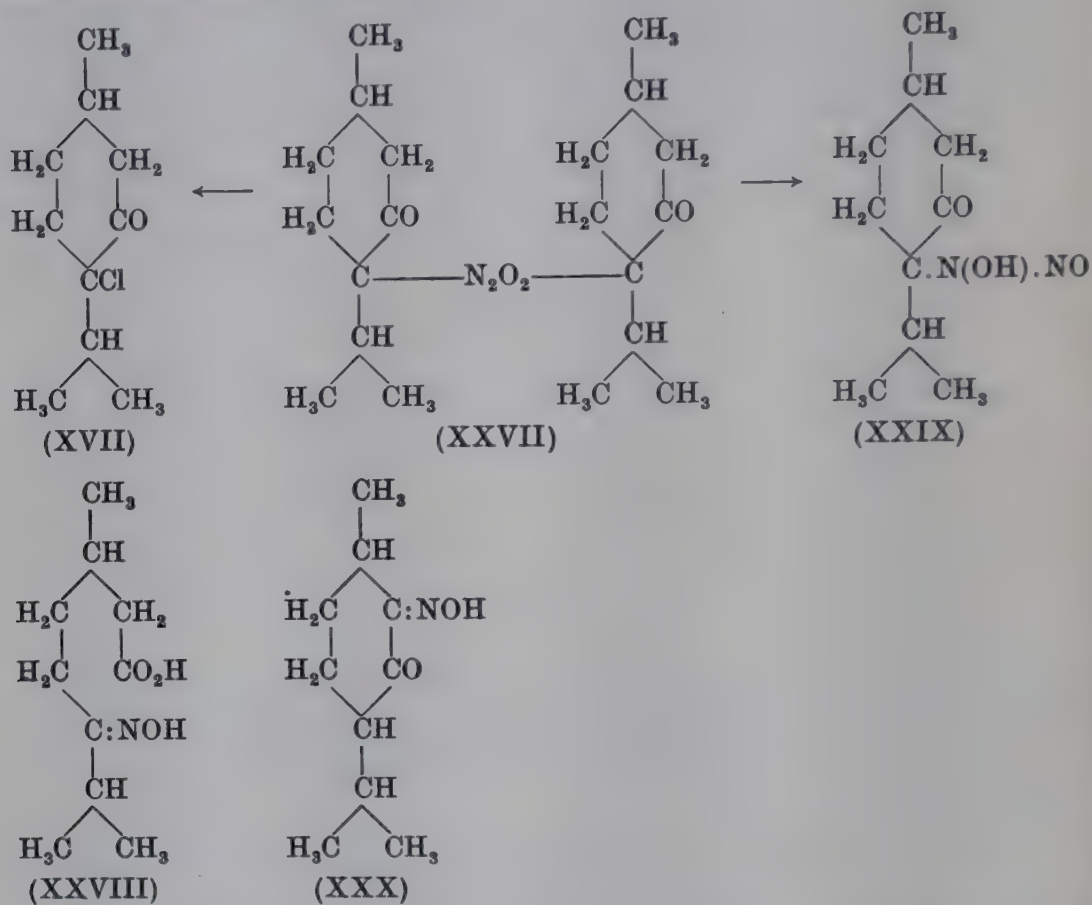
† *Ber.* 1901, 34, 40.

‡ Berkenheim, *Ber.* 1892, 25, 694.

§ Baeyer and Manasse, *ibid.* 1894, 27, 1912; Baeyer, *ibid.* 1895, 28, 1588; Piloty, *ibid.* 1902, 35, 3090; Wieland, *Annalen*, 1903, 329, 244.

|| *Gazzetta*, 1897, 27, II, 97.

paration of which is described on p. 325. This *nitrosomenthone* is an oil and its constitution would appear to be somewhat doubtful, although, since it is soluble in alkali, it is probably the *isonitroso-derivative* (XXX). It can be reduced with zinc dust and acetic acid to an *amine*.



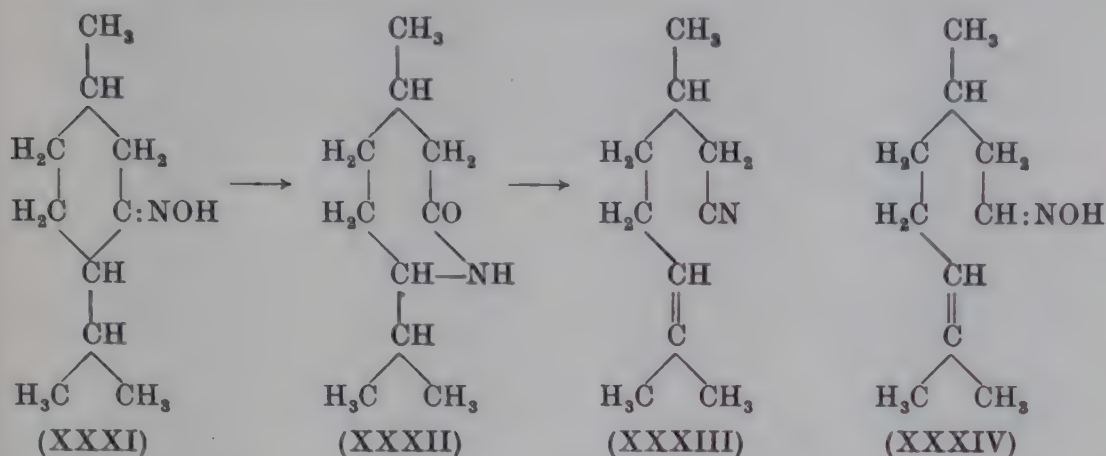
d-4-Nitromenthone, b.p. 135–140°/15 mm., was prepared by Kondakov* by the action of nitric acid on *l*-menthone. Since it is dextrorotatory, it is not improbably a mixture of *l*-4-nitromenthone and *d*-4-nitroisomenthone.

The isomeric menthones react readily with hydroxylamine to yield *oximes*; the melting-points of such as these as are crystalline, together with those of some of their derivatives, are given on p. 241. On reduction the oximes give the isomeric menthylamines (see p. 244).

When *l*-menthoneoxime (XXXI) is treated with phosphorus pentachloride in chloroform solution or with concentrated sul-

* *J. Russ. Phys. Chem. Soc.* 1895, 27, 410; Konowalov and Ischewski, *Ber.* 1898, 31, 1478.

phuric acid, it is converted into an *isoxime*, m.p. 119–120°, $[\alpha]_D - 52.5^\circ$. This interesting substance, which undoubtedly has the structure represented by (XXXII), has been investigated mainly by Beckmann* and Wallach.†



When the isoxime is allowed to react with an excess of phosphorus pentachloride ring fission takes place with the formation of an unsaturated *nitrile*, b.p. 225–226°, from which an *amide*, m.p. 105–106°, and an *acid*, b.p. 257–261°, can be prepared. This nitrile has been represented by the formula (XXXIII), and if this be correct, it should be identical with the nitrile of citronellic acid, which can be prepared from citronellal oxime (XXXIV).‡ This nitrile, which can be characterised by the preparation of a crystalline *nitrosochloride*, m.p. 96–97°,§ does not, however, appear to be identical with the nitrile derived from citronellal. On reduction with sodium and alcohol, it yields the corresponding *amine* (XXXV), which by the action of nitrous acid can be converted into an alcohol, *menthocytronellol* (XXXVI), and this in turn can be oxidised to *menthocytronellal* (XXXVII). A direct comparison of the derivatives of menthocytronellol and menthocytronellal with those of citronellol and citronellal, both of the racemic and optically active modifications, has shown them to be different and the constitutional formulae given to

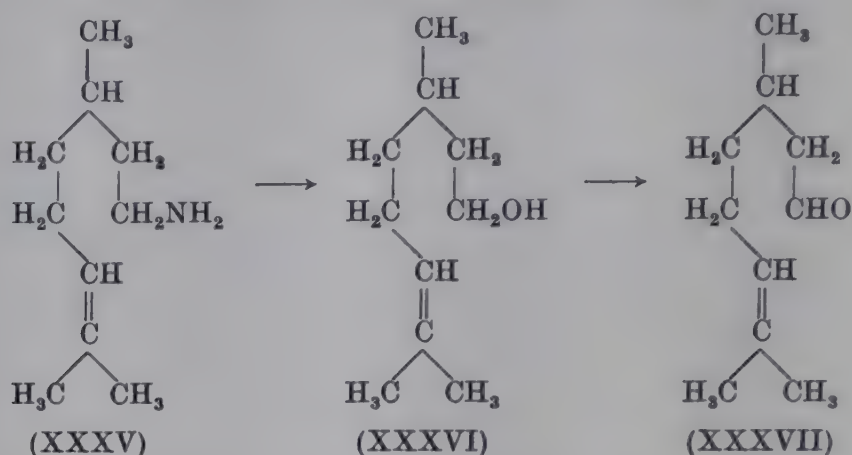
* Beckmann and Mehrländer, *Ber.* 1887, **20**, 1508; *Annalen*, 1896, **289**, 381.

† *Annalen*, 1893, **277**, 156; 1894, **278**, 308; 1899, **309**, 1; 1900, **312**, 197; 1902, **324**, 301.

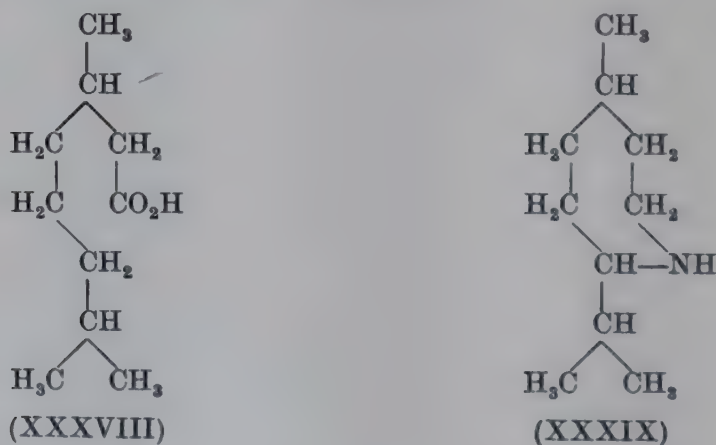
‡ For reasons given on p. 74 this oxime, and therefore probably the nitrile prepared therefrom, is a mixture of two oximes having the ethylenic linkage in the Δ^1 - and Δ^2 -positions.

§ Wallach and Henjes, *Annalen*, 1911, **379**, 227.

them can only be regarded as provisional pending a direct determination of the position of the ethylenic linkage.



When menthoneisoxime* is digested with concentrated potassium hydroxide solution at 220–230° it gives a saturated acid, 2:6-dimethyloctane-8-carboxylic acid (XXXVIII), b.p. 249–251°, whilst by reduction with sodium in amyl alcoholic solution, the cyclic amine (XXXIX) can be prepared.



Amongst other derivatives of menthone may be mentioned the hydrazone, b.p. 144°/30 mm., which according to Kishner.[†] gives, when distilled with potassium hydroxide, *p*-menthane. If the hydrazone is distilled over nickel in a current of hydrogen at 280°, a menthylamine is obtained together with a little menthone and dimethylamine.[‡]

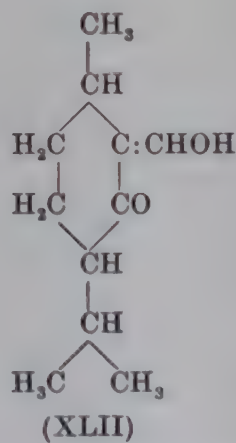
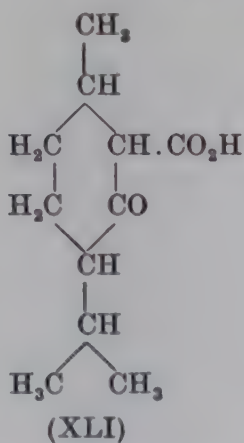
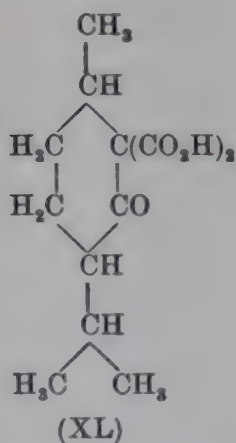
* Wallach, *Annalen*, 1897, **296**, 126; 1912, **389**, 197.

[†] *J. Russ. Phys. Chem. Soc.* 1912, **44**, 1754.

[‡] Maible and Murat, *Bull. Soc. chim.* 1911 [iv], **9**, 467.

Houben and Pfankuch* described the preparation of a stable *menthonecyanohydrin*. It has, however, been shown very conclusively by Lapworth, Manske and Robinson,[†] that this substance cannot have the structure assigned to it. Although menthonecyanohydrin is formed by the action of potassium cyanide on the ketone under suitable conditions, it cannot be isolated in a pure state. It is very unstable and is decomposed by both acids and bases with regeneration of the parent ketone.

Since menthone, in addition to the carbonyl group, contains a reactive methylene group, a number of derivatives involving this group has been prepared. Haller and his collaborators[‡] have shown that in the presence of sodamide it condenses readily with alkyl halides to yield mono-, di- and tri-alkyl menthones. With carbon dioxide in the presence of the same reagent, Gardner, Perkin and Watson[§] obtained a mixture of a *menthone dicarboxylic acid* (XL) and a *monocarboxylic acid* (XLI). Both of these acids are dextrorotatory and are actually derivatives of *d*-isomenthone, inversion occurring during the reaction.



Hydroxymethylenementhone (XLII) was prepared by Bishop, Claisen and Sinclair^{||} by the interaction of *l*-menthone with amyl formate in the presence of sodium. Although Semmler and Mackenzie[¶] have shown that on oxidation with potassium permanganate it gives diosphenol, yet, contrary to anticipation,

* *Ber.* 1927, **60**, 599; compare Passerini, *ibid.* p. 1201.

† *J.C.S.* 1927, p. 2052.

‡ *Compt. rend.* 1904, **138**, 1139; 1913, **156**, 1204.

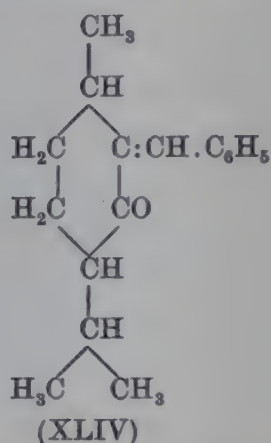
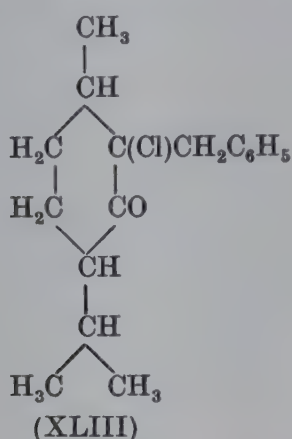
§ *J.C.S.* 1910, **97**, 1760; compare Brühl, *Ber.* 1891, **24**, 3396; Oddo, *Gazzetta*, 1897, **27**, II, 97.

|| *Annalen*, 1894, **281**, 394.

¶ *Ber.* 1906, **39**, 1169.

with ozone, ring fission occurs and α -methyl- α' -isopropyladipic acid is obtained.*

Benzylidenementhone (XLIV), b.p. 188–189°/12 mm., was prepared originally by Wallach,[†] who, by the condensation of *l*-menthone with benzaldehyde in the presence of hydrogen chloride, obtained a *hydrochloride*, m.p. 140°, which undoubtedly has the constitution represented by (XLIII),[‡] and this gives the benzylidene derivative on treatment with sodium ethoxide. Subsequently Martine,[§] by the condensation of the sodium



derivative of *l*-menthone with benzaldehyde, prepared two benzylidenementhones, m.p. 51°, $[\alpha]_D - 185.5^\circ$ (in alcohol) and m.p. 47°, $[\alpha]_D - 258^\circ$ (in alcohol). These two derivatives are probably stereoisomerides, as they give with hydrogen chloride a hydrochloride, m.p. 140°, identical with that obtained by Wallach. More recently, Read, Smith and Hughesdon^{||} prepared 2-benzylidene-dl-isomenthone hydrochloride, m.p. 119–120°. This, by the action of sodium ethoxide, gives a liquid benzylidene-dl-isomenthone, b.p. 193–195°/12 mm. On catalytic hydrogenation, a 2-benzyl-dl-isomenthone, b.p. 195–197°/20 mm., is obtained: the corresponding 7-benzyl-derivative can be prepared by the hydrogenation of benzylidene-dl-piperitone (p. 368). These can readily be differentiated in that the 7-benzyl-derivative will react with semicarbazide, yielding a semicarbazone, m.p. 170–171°, whereas the 2-benzyl-derivative will not.

* Rupe and Gubler, *Helv. Chim. Acta*, 1926, **9**, 582.

† *Ber.* 1896, **29**, 1599.

‡ Boedtker, *Bull. Soc. chim.* 1915 [iv], **17**, 374.

§ *Compt. rend.* 1901, **133**, 41; 1902, **134**, 1437; 1905, **140**, 130.

|| *J.C.S.* 1924, **124**, 133.

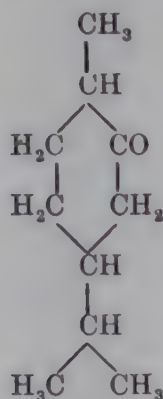
The action of the Grignard reagent on benzylidenementhone was investigated by Boedtke,* who showed that addition takes place at the ethylenic linkage, the carbonyl group being unaffected. The reaction is thus analogous to that of hydroxylamine, which was shown by Semmler† to give not an oxime but a hydroxylamine derivative.

In addition to the reactions described above, menthone has been used in a large number of synthetic operations, since it reacts readily with the Grignard reagent or with halide esters in the presence of zinc.

CARVOMENTHONE

(TETRAHYDROCARVONE)

(p-Menthan-2-one or 1-Methyl-4-isopropylcyclohexan-2-one)



The occurrence in nature of *l*-carvomenthone, $C_{10}H_{18}O$, has been recorded by Simonsen and Rao,‡ who separated it from the oil obtained from the shrub *Blumea Malcomii*. It is found also in *Blumea eriantha*.§

The ketone (II) was prepared practically simultaneously by Baeyer|| and Wallach¶ by the oxidation of the corresponding secondary alcohol, *carvomenthol* (I), thus affording direct proof of its constitution. It is a colourless oil, with an odour reminiscent of both carvone and menthone. For the natural *l*-carvo-

* *Compt. rend.* 1912, 154, 437.

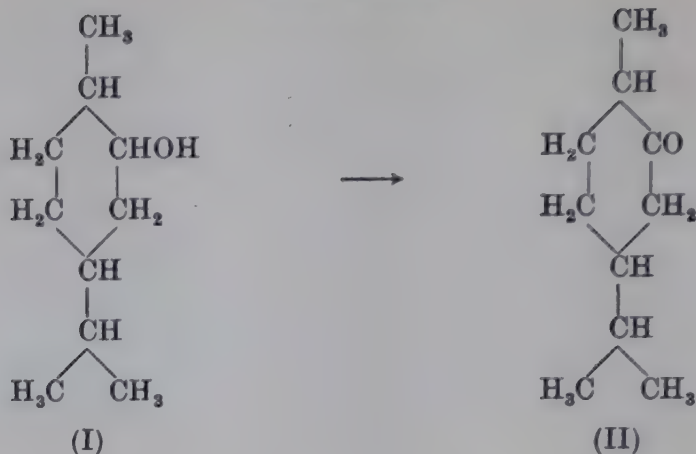
‡ *J.C.S.* 1922, 121, 881.

|| *Ber.* 1893, 26, 822.

† *Ber.* 1904, 37, 234.

§ *Schimmel's Report*, 1937, p. 8.

¶ *Annalen*, 1893, 277, 133.



menthone Simonsen and Rau found the following constants: b.p. 218.6–219°/705 mm., d_{30}^{30} 0.9001, n_D^{30} 1.4531, $[\alpha]_D^{30}$ -9.33° , whilst for the *dl*-form prepared from *dl*-carvomenthol Wallach* gave b.p. 220–221°, d^{20} 0.90, n_D^{20} 1.4554.

Carvomenthone has been identified by the preparation of the *oxime* (*d*- and *l*-forms, m.p. 97–99°; *dl*-, m.p. 105°), or of the *semicarbazone* (*d*- and *l*-forms, m.p. 194–195°; *dl*-, m.p. 174°), but these derivatives are not necessarily stereochemical individuals, since the ketone itself can exist in *cis*- and *trans*-forms. According to Johnston and Read,[†] who prepared the two modifications of the ketone by the oxidation of the corresponding carvomenthols (see p. 251), the *trans*-form, *l*-carvomenthone, has d_4^{20} 0.9000, n_D^{17} 1.4548, $[\alpha]_D^{17}$ -6° (*semicarbazone*, m.p. 192°, $[\alpha]_D$ -13.3° in chloroform) and the *cis*-isomeride, *l*-isocarvomenthone, has d_4^{20} 0.9102, n_D^{20} 1.4558, $[\alpha]_D^{20}$ -56.5° (*semicarbazone*, m.p. 171–172°, $[\alpha]_D$ -117° in chloroform). The *oximes* have been investigated by Hückel and Doll,[‡] who have isolated the *syn*- and *anti*-forms from each modification of the ketone. *l*-Carvomenthone gives *oxime* I, m.p. 100–101°, $[\alpha]_D$ -42.3° , and *oxime* II, m.p. 30–32°, $[\alpha]_D$ $+91.2^\circ$, whilst *l*-isocarvomenthone gives *oxime* I, m.p. 64–65°, $[\alpha]_D$ -72.5° , and *oxime* II, m.p. 30–31°, $[\alpha]_D$ -65.5° .

In addition to its preparation by the oxidation of carvomenthol, the ketone has been obtained by the hydrogenation of carvone, carvoxime, carvotanacetone, dihydrocarvone and

* *Annalen*, 1893, **277**, 133; *Ber.* 1895, **28**, 1962.

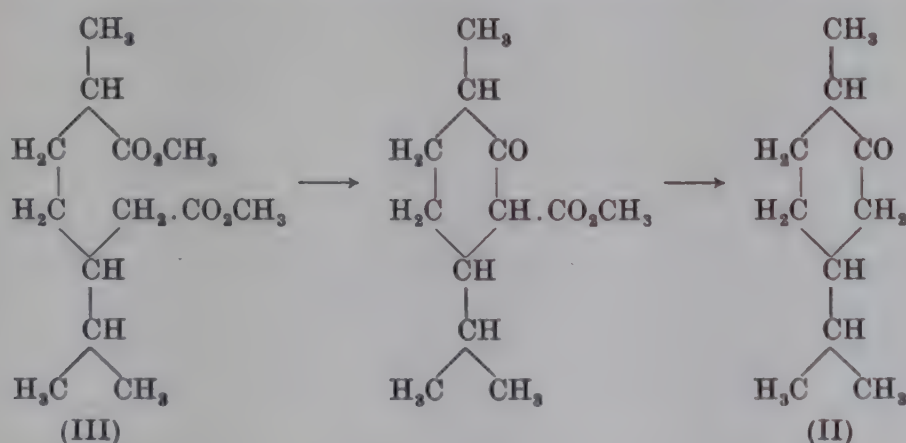
† *J.C.S.* 1935, p. 1138.

‡ *Annalen*, 1936, **526**, 103. For earlier investigations on carvomenthone oxime and semicarbazone, see Baeyer, *Ber.* 1895, **28**, 1600; Wallach, *Annalen*, 1893, **277**, 134; 1895, **287**, 159, 377; 1900, **312**, 203; 1902, **323**, 332.

carvenone under a variety of conditions which are discussed elsewhere. According to Wallach* it can be prepared most advantageously by the catalytic hydrogenation of either carvenone or dihydrocarvone. Attention may be directed here to the observation of Vavon,[†] that *d*-carvotanacetone yields on reduction *l*-carvomenthone, which is of interest since these two ketones are associated in nature.

Mention has been made already of the conversion of *l*- α -phellandrene nitrosite into carvomenthone (p. 196); of particular interest also is its formation by the action of amyl formate in the presence of sodium on the dicyclic ketone, carone, when the sodium salt of the hydroxymethylene derivative of the dicyclic ketone, the primary product of the reaction, decomposes on warming with formation of the saturated monocyclic ketone.

Carvomenthone was also prepared by Ruzicka and Trebler[‡] by the action of sodium on *methy*l α -*methy*l- α' -isopropyladipate (III) by the reactions indicated in the scheme set out below.



By the catalytic hydrogenation of carvone under diminished pressure, and subsequent acetylation of the products, Grignard and Mingasson[§] prepared the *acetate* of the *enolic* form of carvomenthone. This is an oil, b.p. 103–105°/11 mm., $d_4^{13^\circ}$ 0.947, $n_D^{13^\circ}$ 1.4619, whilst the *enol* itself, which is extremely unstable, being ketonised in one hour, has b.p. 104–106°/11 mm., n_D 1.4624.

By the action of reducing agents, carvomenthone is converted into carvomenthol, but Ipatiev^{||} has recorded its complete

* *Annalen*, 1918, **414**, 274.

‡ *Helv. Chim. Acta*, 1920, **3**, 779.

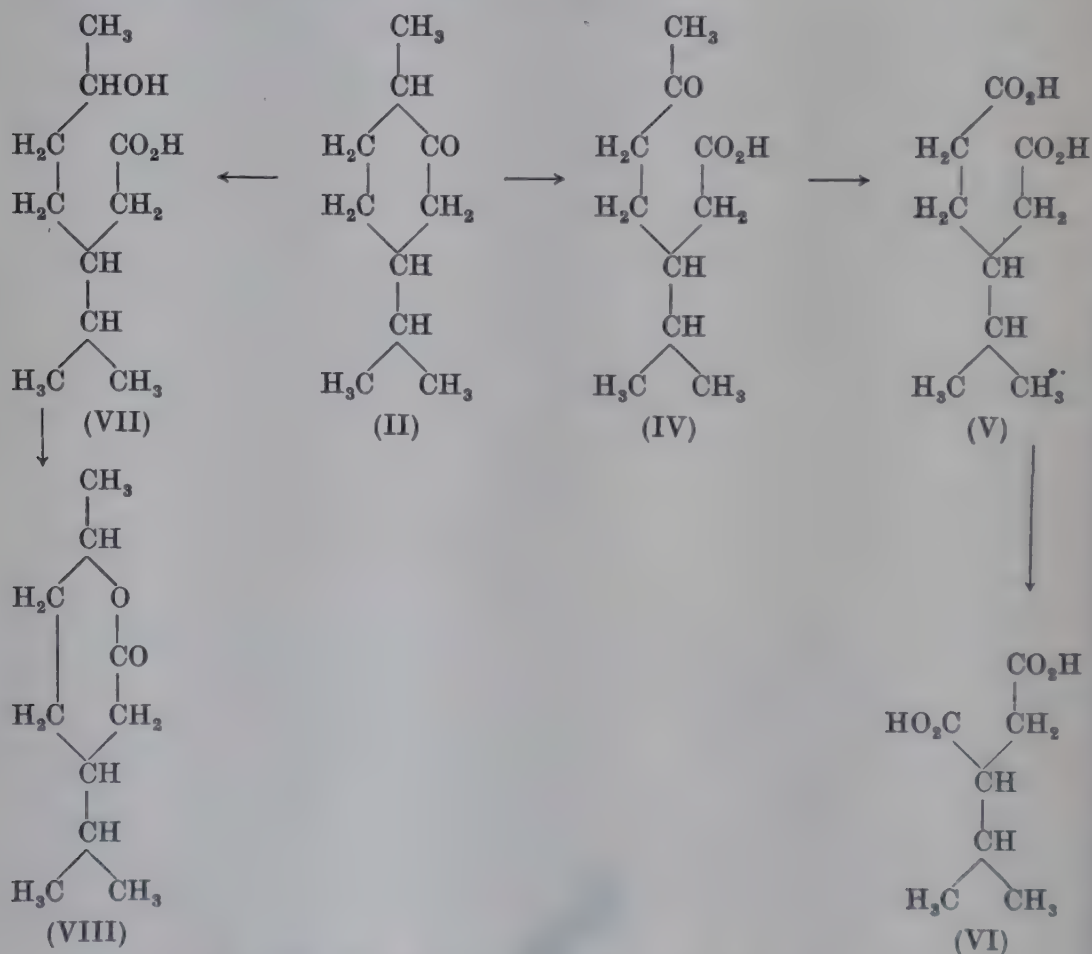
|| *Ber.* 1912, **45**, 3212.

† *Compt. rend.* 1911, **153**, 70.

§ *Compt. rend.* 1927, **185**, 1556.

reduction to *p*-menthane by treatment with hydrogen under pressure in the presence of a nickel-alumina catalyst.

The oxidation of carvomenthone has been studied mainly by Baeyer and his collaborators.* With potassium permanganate at 40–45°, the main product of the reaction is 2-isopropylhexan-5-one carboxylic acid (IV), m.p. 40° (*semicarbazone*, m.p. 152–153°); when, however, the reactants are heated to boiling, isopropylsuccinic acid (VI) was obtained, β -isopropyladipic acid (V) being evidently an intermediate product. The ketonic acid (IV) is formed also on oxidation of the ketone with chromic acid[†] or with hydrogen peroxide in the presence of vanadium pentoxide.[‡] By the action of Caro's reagent the *lactone* (VIII) of the hydroxy-acid (VII) is obtained. Dehydrogenation of carvomenthone with palladium gives carvacrol.[§]



* *Ber.* 1896, **29**, 36; 1899, **32**, 3629; 1900, **33**, 124.

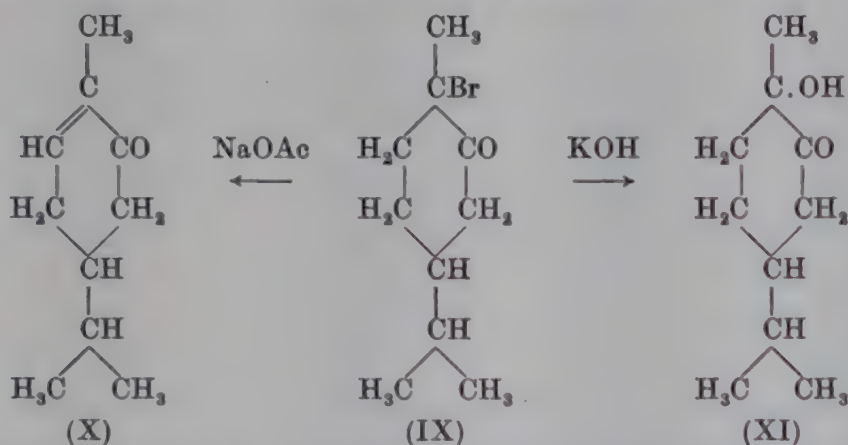
† Wallach and Koller, *Annalen*, 1905, **339**, 113.

‡ Treibs, *Ber.* 1939, **72**, 1199.

§ Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

In addition to the products which can be prepared by the direct halogenation of carvomenthone, which must be considered now, others can be prepared indirectly from the unsaturated ketones, dihydrocarvone, carvenone and carvotanacetone, and are discussed elsewhere.

The bromination of the ketone has been investigated by Kötze and Steinhorst* and by Wallach.† By the action of one molecule of bromine in acetic acid solution, a *monobromide*, b.p. 138–140°/14 mm., is first formed, which must be 1-bromo-p-menthan-2-one (IX), since it is converted by the action of sodium acetate in acetic acid solution into *carvotanacetone* (X) and by the action of cold dilute alkali into the *hydroxy-ketone* (XI).



With two molecules of bromine a liquid *dibromide* is obtained, which must be 1:3-dibromo-p-menthan-2-one (XII), since, on digestion with potassium hydroxide solution, it gives a mixture of the isomeric *hydroxy-ketones*, m.p. 81–82° (XIII) (diosphenol) and m.p. 36–37° (XIV), the formation of which from dibromomenthone is discussed on p. 319. The *hydroxycyclopentane acid* (XV) is also formed.‡ The probable mechanism involved in the formation of these substances is shown in the scheme set out on p. 332.

With sodium hydrogen sulphite carvomenthone forms an extremely unstable compound which is immediately decomposed by water,§ but it forms crystalline salts with ferro- and ferrihydrocyanic acids.||

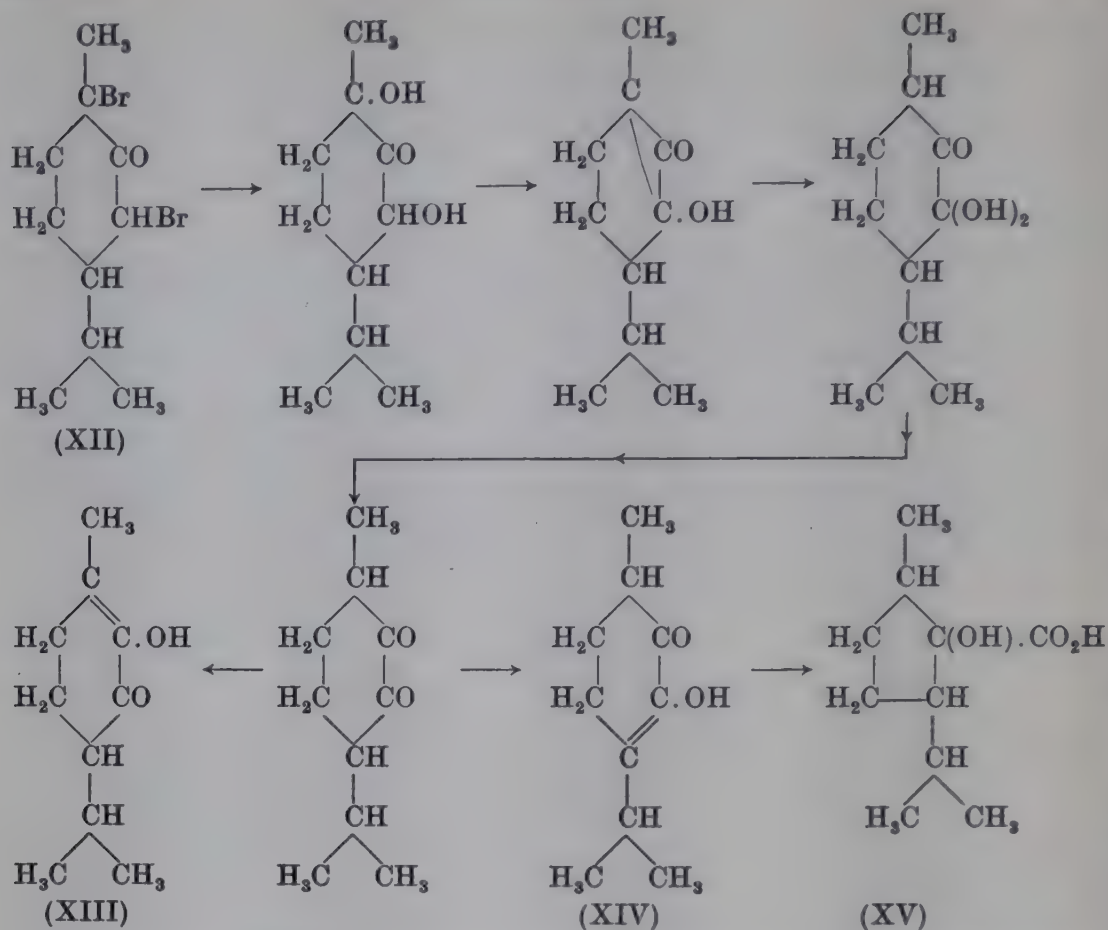
* *Annalen*, 1911, **379**, 13.

† *Ibid.* 1918, **414**, 279, 349, 353.

‡ Compare Cusmano and Poccianti, *Atti R. Accad. Lincei*, 1914 [v], **23**, I, 347.

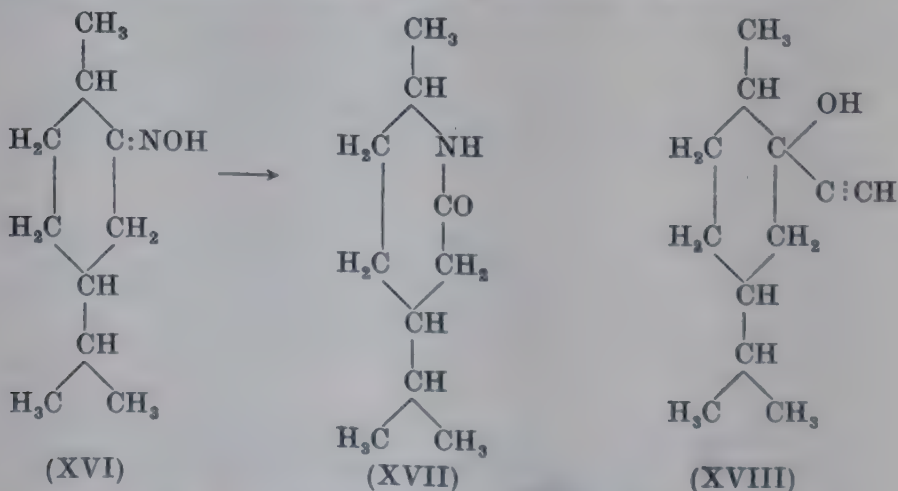
§ Baeyer, *Ber.* 1893, **26**, 822.

|| Baeyer and Villiger, *ibid.* 1901, **34**, 2679.



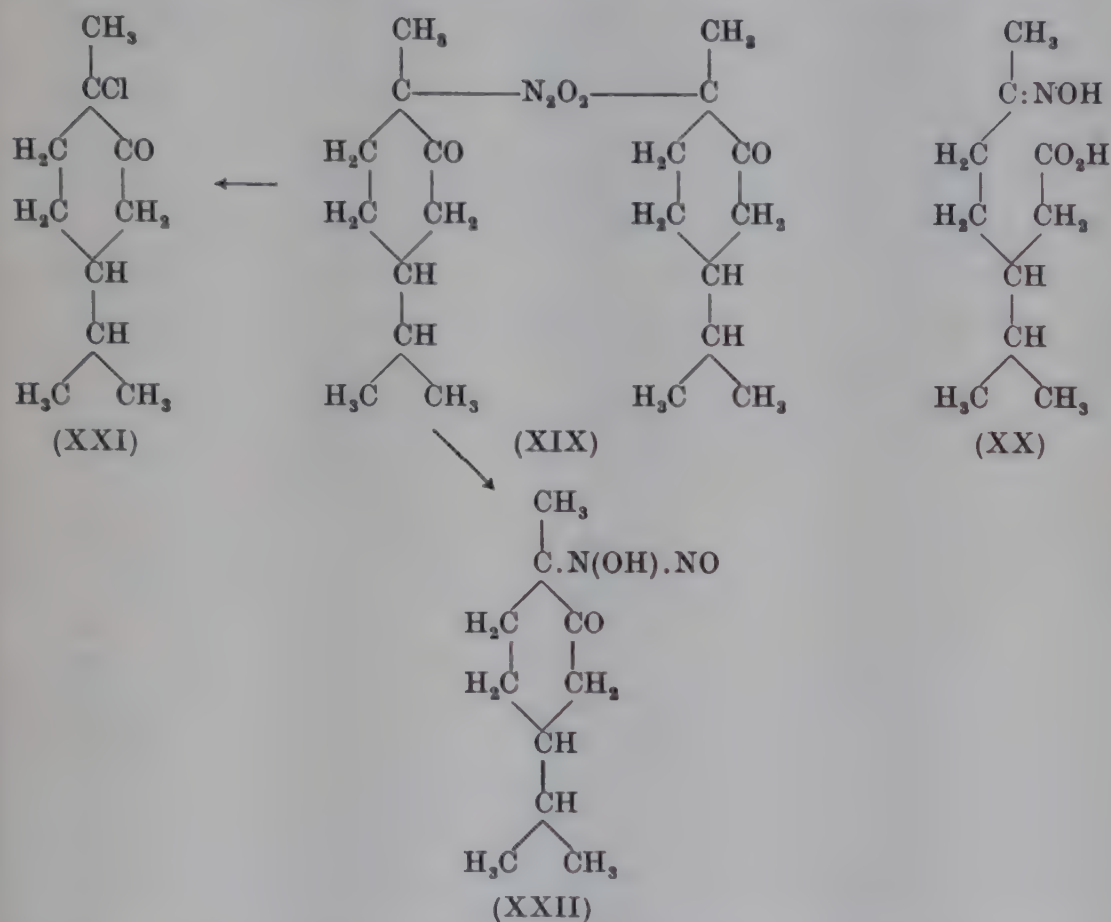
The oxime (XVI) on treatment with phosphorus pentachloride or with sulphuric acid in acetic acid solution gives the *lactam* of ϵ -amino- β -isopropylheptoic acid (XVII), which exists in two forms, m.p. 51–52° and 102°.

The *acetylenecarbinol* (XVIII) is obtained by condensation of the ketone with acetylene in the presence of sodium.*



* Rupe and Kuenzy, *Helv. Chim. Acta*, 1931, 14, 708.

By the action of nitrous acid on carvomenthone, a highly characteristic *nitroso*-derivative (XIX), m.p. 119°, is obtained, which is probably bimolecular.* The yield of the nitroso-body, which is prepared by the action of amyl nitrite and acetyl chloride on the ketone, is small since it tends to pass very readily into the ϵ -oximinic- β -isopropylheptoic acid (XX), and this is the

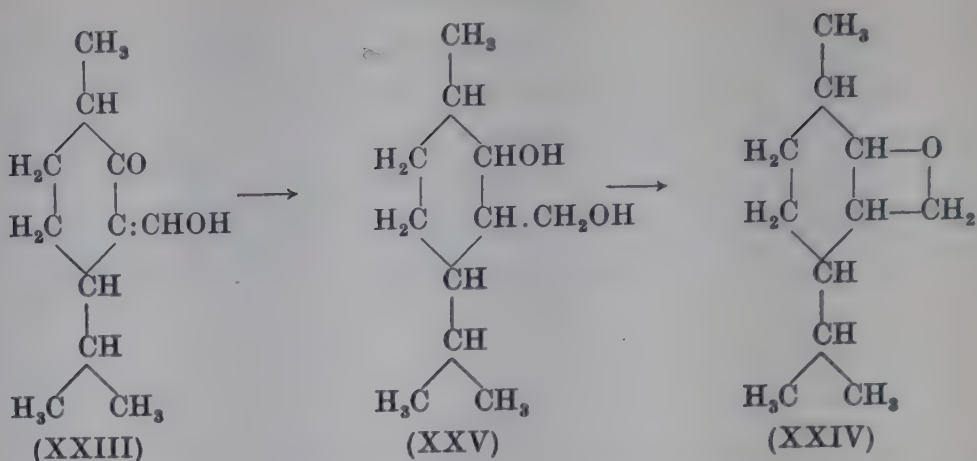


main product if hydrogen chloride is used in place of acetyl chloride to decompose the amyl nitrite. Bis-nitrosocarvomenthone is decomposed by hydrogen chloride in ethereal solution to yield 1-chloro-p-menthan-2-one (XXI) and the *nitrosylic acid* (XXII).

Hydroxymethylenecarvomenthone (XXIII) has been prepared by Rupe and Schäfer.[†] On hydrogenation it yields the *oxide* (XXIV), presumably formed via the *diol* (XXV).

* Baeyer, *Ber.* 1895, **28**, 1588; Baeyer and Oehler, *ibid.* 1896, **29**, 27; Piloty, *ibid.* 1902, **35**, 3090; Wieland, *Annalen*, 1903, **329**, 244.

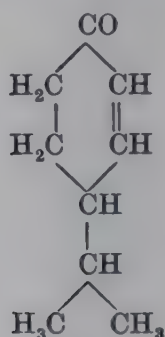
[†] *Helv. Chim. Acta*, 1928, **11**, 470.



The absorption spectrum of carvomenthone has been studied by Lowry and Lishmund* and by Cooke and Macbeth.†

CRYPTONE

(4-isoPropyl- Δ^2 -cyclohexen-1-one)



Although the ketone, 4-isopropyl- Δ^2 -cyclohexen-1-one, C₉H₁₄O (I), now designated *cryptone*, was first obtained by Wallach‡ by the air oxidation of β -phellandrene (II) in sunlight and later by the action of dilute sulphuric acid on nopinone (III) and sabinaketon (IV),§ its occurrence in nature was first observed by Cahn, Penfold and Simonsen,|| who separated the laevorotatory form of the ketone from the oils from *Eucalyptus cneorifolia*, *E. hemiphloia* and *E. polybractea*. Some years later the dextro-rotatory form was shown independently by Berry, Macbeth and Swanson¶ and by Wienhaus and Striegler** to occur in water fennel oil from *Phellandrium aquaticum*.

* J.C.S. 1935, p. 1313.

‡ *Annalen*, 1905, **343**, 30.

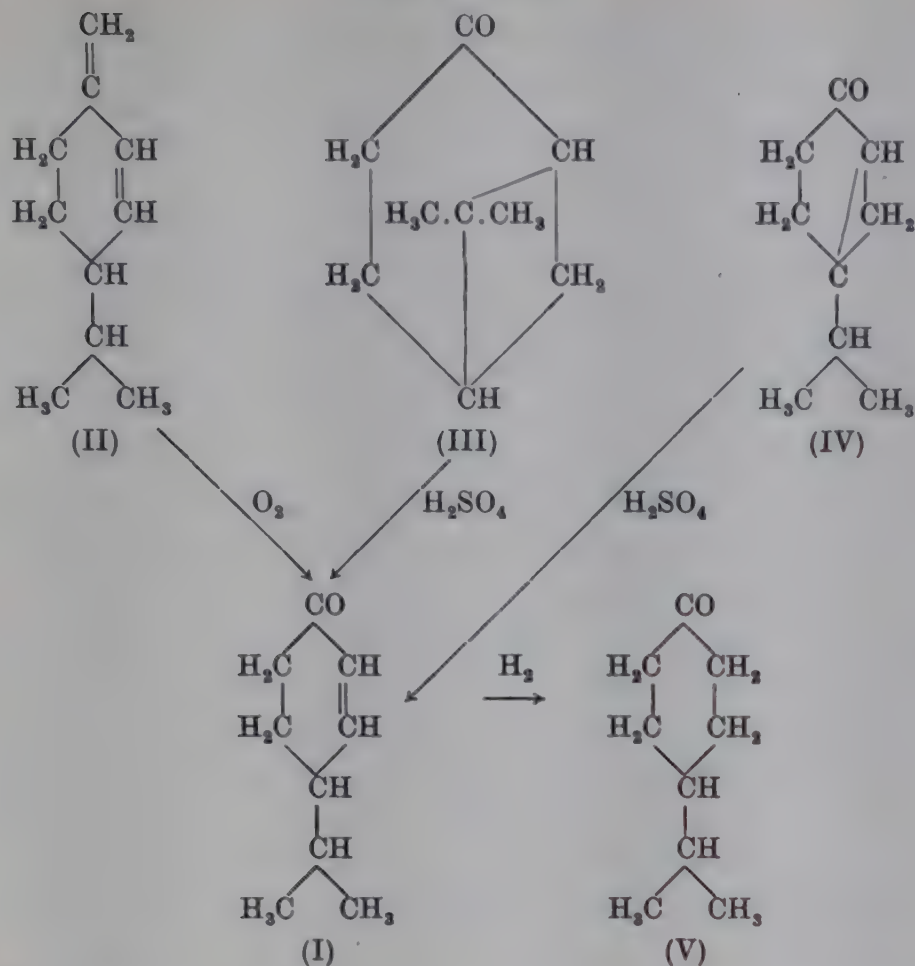
§ *Ibid.* 1907, **356**, 235; 1908, **359**, 270.

¶ *Ibid.* 1937, p. 1448.

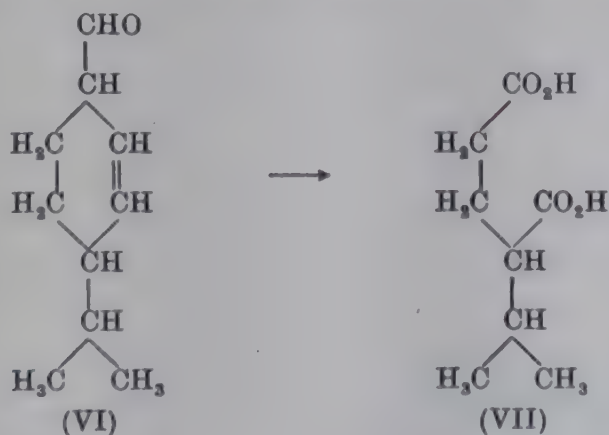
† *Ibid.* 1938, p. 1408.

|| J.C.S. 1931, p. 1366.

** *Schimmel's Report*, 1937, p. 91.



The identity of the natural ketone with that described by Wallach was established by Cahn, Penfold and Simonsen by the preparation of its hydrogen sulphide derivative and by its hydrogenation to 4-isopropylcyclohexan-1-one (V). It has been shown by Berry, Macbeth and Swanson* that the aldehyde, 1-*cryptal* (VI), described by Penfold and Simonsen† and which gives on



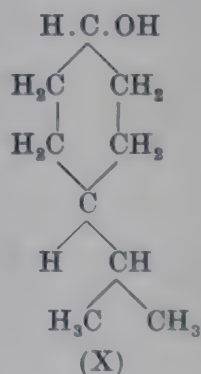
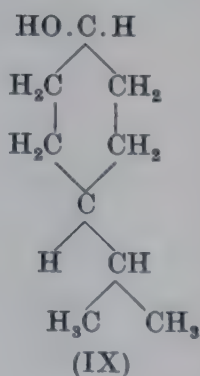
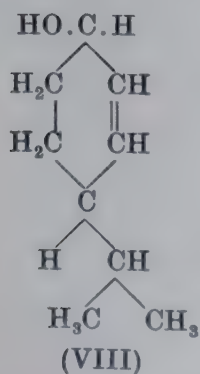
* *J.C.S.* 1937, pp. 986, 1443.

† *Ibid.* 1930, p. 403.

oxidation with potassium permanganate *d*- α -isopropylglutaric acid (VII) was actually *l*-cryptone, which would give the same acid on oxidation. The aldehyde, therefore, does not occur in nature.

l-Cryptone from the eucalyptus oils had b.p. 98–100°/10 mm., d_{15}^{15} 0.9472–0.9483, n_D^{20} 1.4820–1.4848, α_D –59.3 to –66.4°, *semi-carbazone*, m.p. 185°, *hydrosulphide*, m.p. 206–207°.* The optically pure ketone, b.p. 90°/9 mm., n_D^{18} 1.4841, $[\alpha]_D$ –119.3° (in alcohol), 2:4-dinitrophenylhydrazone, m.p. 132°, was first prepared by Galloway, Dewar and Read† by the oxidation with chromic acid of *l*-cryptol (VIII), which can be readily obtained by the reduction of the ketone with the Ponndorf reagent. The alcohol, purified through its *p*-nitrobenzoate, m.p. 84°, $[\alpha]_D$ –168.5° (in chloroform), had b.p. 97°/8 mm., n_D^{21} 1.4721, $[\alpha]_D$ –139.3° (in alcohol) and was characterised by the preparation of its 3:5-dinitrobenzoate, m.p. 115°, *phenylurethane*, m.p. 105°, and its α -*naphthylurethane*, m.p. 118°.* The dextrorotatory alcohol, b.p. 72°/2 mm., n_D^{20} 1.4796, $[\alpha]_D$ +146.4°, was prepared by Macbeth and Winzor‡ from *d*-cryptone in a similar manner. According to Wienhaus and Striegler|| this alcohol is present in water fennel oil.

As has been shown by Macbeth and Winzor, cryptol must have the *trans*-configuration (VIII), since on catalytic hydrogenation both the *d*- and *l*-alcohols yield *trans*-dihydrocryptol (IX). This alcohol and its *cis*-epimer (X) have been studied by Cooke, Gillespie and Macbeth§ and their physical constants



* Hooper, Macbeth and Price, *J.C.S.* 1934, p. 1149.

† *Ibid.* 1936, p. 1595.

‡ Gillespie, Macbeth and Swanson, *ibid.* 1938, p. 1820.

§ *Ibid.* 1939, p. 264.

|| *J.C.S.* 1939, p. 518.

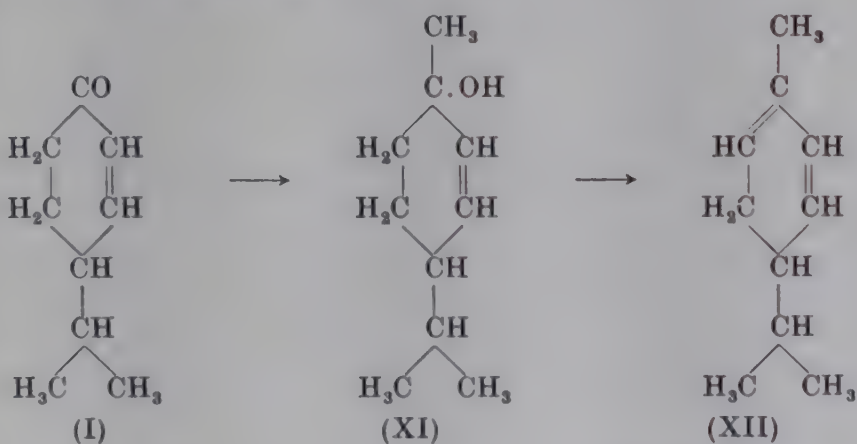
|| *Loc. cit.*

together with those of some of their derivatives are given in Table I.

Table I

<i>cis</i> -Dihydrocryptol	<i>trans</i> -Dihydrocryptol
d_{20}^{20} 0.9212	0.9156
n_D^{20} 1.4671	1.4658
Phenylurethane, m.p. 130°	114.5°
α -Naphthylurethane, m.p. 113°	159.5°
<i>p</i> -Nitrobenzoate, m.p. 69.5°	75-75.5°
3:5-Dinitrobenzoate, m.p. 112°	124.5°

Since β -phellandrene (II), which may be regarded as the precursor in nature of cryptone, has been shown by Berry, Macbeth and Swanson* to be present in eucalyptus oils containing the ketone, the quantity varying seasonally, it is of considerable interest that Galloway, Dewar and Read† have found that 1- α -phellandrene (XII) results from the dehydration of the *p*-menthenol (XI), which is formed when cryptone is treated with methyl magnesium iodide.

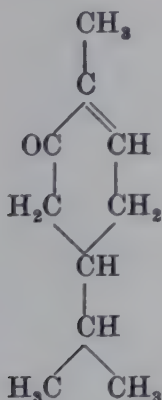


* *Loc. cit.*

† *Loc. cit.*

CARVOTANACETONE

(Δ^1 -p-Menthen-6-one or
1-Methyl-4-isopropyl- Δ^1 -cyclohexen-6-one)



In 1894 Semmler* observed that when the saturated dicyclic ketone α -thujone was heated in a sealed tube at 280° it underwent a molecular rearrangement with formation of a new unsaturated ketone, $C_{10}H_{16}O$, to which he gave the name *carvotanacetone*. The ketone, which was optically inactive, was characterised by the preparation of the *oxime*, m.p. $92-93^\circ$. In the previous year Wallach† had separated from the high boiling fraction of thuja oil (from *Thuja occidentalis*) a ketone yielding an oxime of this melting-point, and this ketone was subsequently recognised as being identical with Semmler's carvotanacetone. It remains doubtful, however, whether it exists preformed in thuja oil or whether it is formed from thujone during the process of purification.

The existence of carvotanacetone in nature was first definitely established by Simonsen and Rau,‡ who separated *d*-carvotanacetone from the oil derived from the small herb *Blumea Malcomii*, which occurs in the western part of the Deccan plateau at elevations of over 2000 feet; more recently it has been found in *Blumea eriantha*.§

The constitution of carvotanacetone was determined by Semmler,|| who showed that on oxidation with potassium permanganate it gave a mixture of *pyruvic acid* (II) and *isopropyl-*

* Ber. 1894, 27, 895.

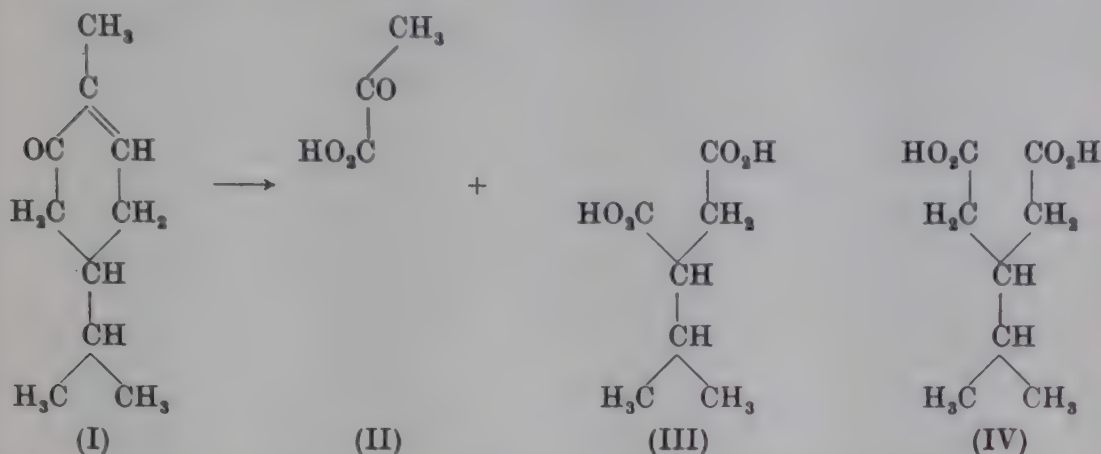
† J.C.S. 1922, 121, 876.

|| Ber. 1900, 33, 2454.

† Annalen, 1893, 275, 182.

§ Schimmel's Report, 1937, p. 8.

succinic acid (III), products which could only result if the ketone was Δ^1 -*p*-menthen-6-one (I). As will be seen, this formula is in full accord with its properties.



By working under what were probably somewhat different conditions, Simonsen and Rau* did not obtain any pyruvic acid by the oxidation of *d*-carvotanacetone with potassium permanganate. They isolated as sole products of the oxidation acetic acid and β -isopropylglutaric acid (IV).

Carvotanacetone has not been prepared by any direct synthesis, but, since it can be obtained from carvone (see below), its indirect synthesis has been accomplished.

Carvotanacetone is an oil possessing an odour indistinguishable from that of carvone. The following are representative constants, which have been observed for the *dl*-, *d*- and *l*-forms of the ketone: *dl*-, b.p. 228–228.5°, d_4^{20} 0.9351, n_D^{20} 1.4805;† *d*-, b.p. 227.5°, d_{30}^{30} 0.9305, n_D^{30} 1.4767, $[\alpha]_D^{30} + 59.5^\circ$;‡ b.p. 227–228°, d^{19} 0.9351, $[\alpha]_D^{25} + 49.5^\circ$;§ *l*-, b.p. 227–229°, d^{15} 0.9345, n_D^{19} 1.4822.¶ It would appear to be probable that the ketone obtained by Simonsen and Rau was nearly optically pure, since Vavon,¶ by the hydrogenation of *d*-carvone, obtained a specimen having an almost identical rotation (+59.8°).

A number of derivatives of carvotanacetone are available for its characterisation, the most suitable probably being the *semi*-carbazone originally prepared by Baeyer.** The *dl*-semicarbazone melts at 177–178°, whilst the *d*- and *l*-forms melt at 173–174°.

* *Loc. cit.*

† Brühl, *Ber.* 1899, 32, 1225.

‡ *J.C.S.* 1922, 121, 876.

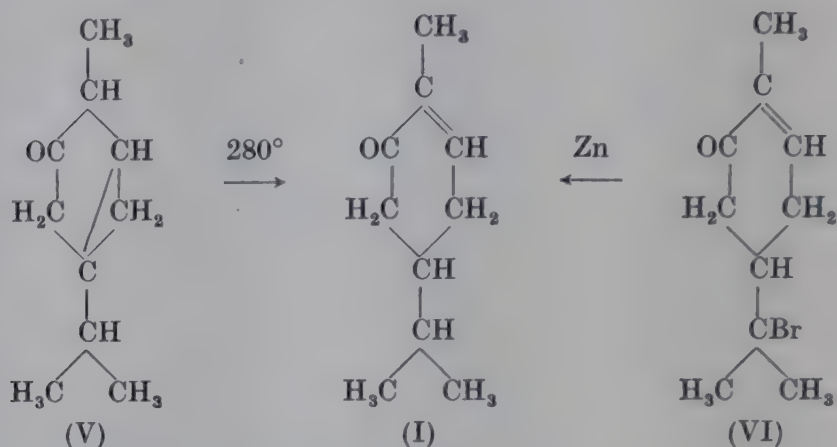
§ Harries and Stirm, *Ber.* 1901, 34, 1929.

¶ Wallach, *Annalen*, 1904, 336, 37.

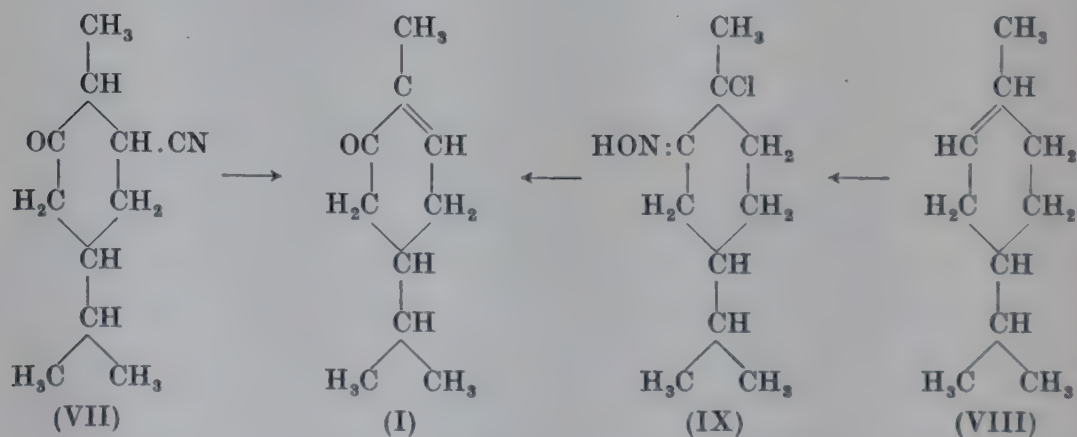
¶ *Compt. rend.* 1911, 153, 70.

** *Ber.* 1894, 27, 1923.

Carvotanacetone has been prepared by a number of methods. As mentioned above, it is formed from α -thujone (V) by molecular rearrangement, a method of preparation, however, which furnishes no proof of its constitution.



d-Carvotanacetone was first prepared by Harries and Stirn* by the reduction of *d*-carvone hydrobromide (VI) with zinc dust in methyl alcoholic solution. Another method for the preparation of the ketone was devised by Lapworth,[†] who showed that cyanocarvomenthone (VII), when heated with a solution of potassium hydroxide containing freshly precipitated ferric hydroxide in suspension, lost hydrogen cyanide with formation of carvotanacetone.

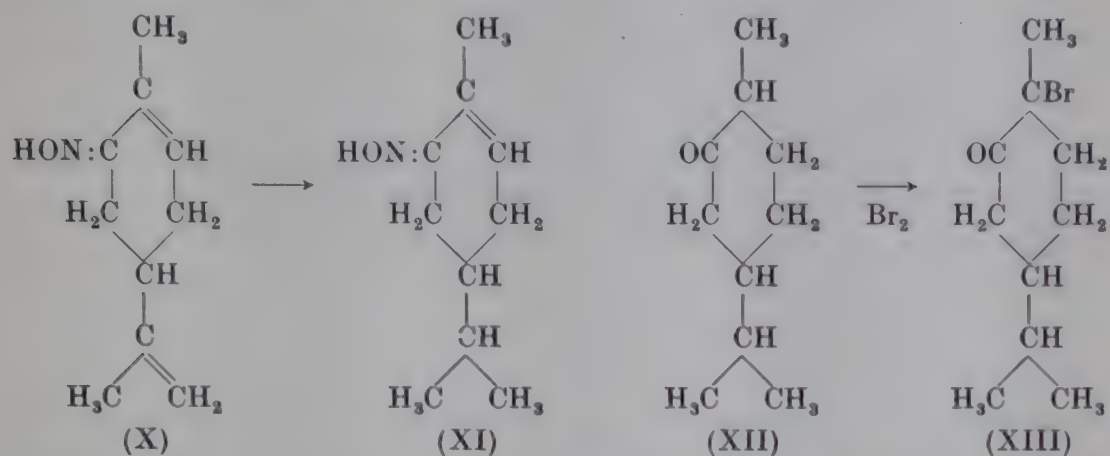


Wallach described three methods for the preparation of the ketone. He showed that when the nitrosochloride (IX) of Δ^1 -p-menthene (VIII) is treated with sodium acetate it yields carvo-

* Ber. 1901, 34, 1929.

† J.C.S. 1906, 89, 945.

tanacetone.* A simpler process consists in the hydrogenation of *carvoxime* (X) in the presence of colloidal palladium, when *carvotanacetoxime* (XI) results.†



Prior to this, Vavon‡ had shown that by the regulated hydrogenation of *d*-carvone in the presence of platinum black *d*-carvotanacetone was formed.

Reference may also be made to the experiments of Wallach§ on the reduction of *l*-nitro- α -phellandrene to *l*-carvotanacetone which have been discussed on p. 198, and to the work of Borgwardt and Schwenk|| who have shown that the ketone is formed by the action of selenium dioxide on Δ^1 -*p*-menthene. According to Tabuteau,¶ carvotanacetol is also formed in this reaction.

For the preparation of carvotanacetone the simplest method would appear to be that devised by Kötze and Steinhorst.** Carvomenthone (XII) on bromination in acetic acid solution yields the *bromide* (XIII), b.p. 138–140°/14 mm., and this, on digestion with sodium acetate in acetic acid solution, gives carvotanacetone in excellent yield.

The action of reducing agents on carvotanacetone was first investigated by Semmler,†† who showed that on treatment with sodium and alcohol, *p*-menthan-2-ol (carvomenthol) (XIV) was formed. This observation was confirmed by Wallach,‡‡ who found

* *Annalen*, 1911, 381, 59.

† *Compt. rend.* 1911, 153, 70.

‡ *J. Amer. C.S.* 1934, 56, 1185.

§ *Bull. Inst. Pin.* 1935, p. 5; *Compt. rend.* 1935, 200, 244.

** *Annalen*, 1911, 379, 13; compare Wallach, *ibid.* 1918, 414, 353.

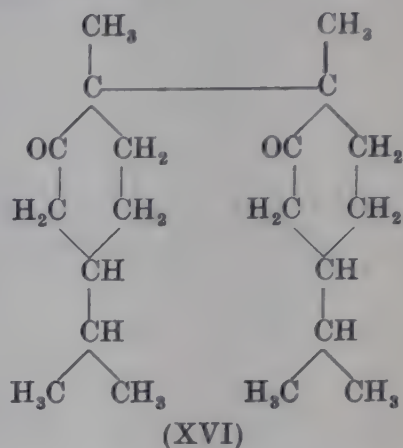
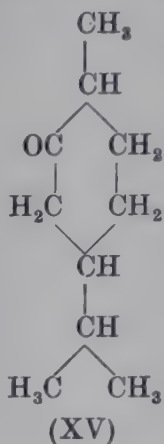
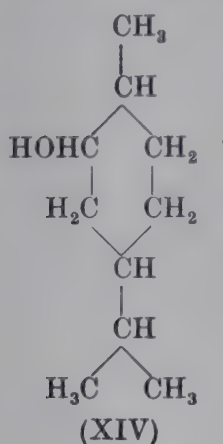
†† *Ber.* 1894, 27, 895.

† *Ibid.* 1914, 403, 74.

§ *Annalen*, 1914, 403, 74.

‡‡ *Ibid.* 1895, 28, 1955.

that oxidation of the secondary alcohol gave the saturated ketone, *p-menthan-2-one* (carvomenthone) (XV).



The action of other reducing agents was investigated by Harries and Stirm,* who found that, whilst reduction of *d*-carvotanacetone with zinc dust in alkaline solution gave *d*-carvomenthone, with aluminium amalgam a *pinacone*, which probably has formula (XVI), was obtained. This ketone could not be crystallised, but it was characterised by the preparation of a sparingly soluble *bis-phenylhydrazone*, m.p. 260°.

It has already been mentioned that carvotanacetol is one of the products formed by the oxidation of Δ^1 -*p*-menthene (carvomenthene) with selenium dioxide. This alcohol should exist in two stereoisomeric *dl*-modifications. By the reduction of *d*-carvotanacetone with aluminium isopropoxide, Read and Swann† obtained a *d*-carvotanacetol, b.p. 101°/13 mm., n_D^{20} 1.4800, α_D^{17} +100.5° (*p*-nitrobenzoate, m.p. 93.5–94°, $[\alpha]_D$ +85°); a *p*-nitrobenzoate, m.p. 60–62°, $[\alpha]_D$ –51.3°, of an isomeric carvotanacetol was also isolated, though the corresponding alcohol was not described.

The catalytic hydrogenation of *d*-carvotanacetone has been studied by Vavon,‡ who showed that *l*-carvomenthone is formed.

The degradation of carvotanacetone on oxidation with potassium permanganate has been discussed above. Autoxidation leads to the formation of the oxide (XVII).§

The action of bromine on *dl*- and *l*-carvotanacetone has been examined by Wallach.|| A liquid *dibromide* (XVIII) is formed

* Ber. 1901, 34, 1933.

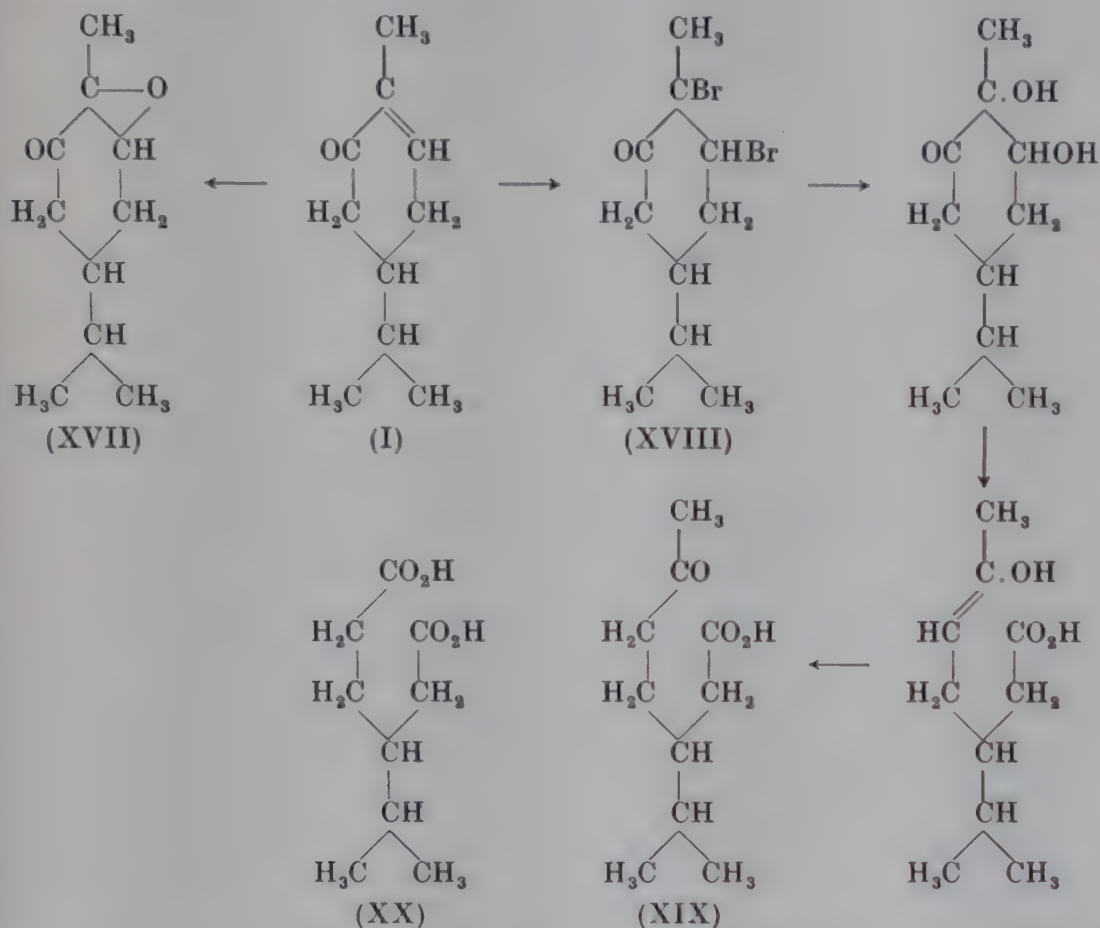
† Compl. rend. 1911, 153, 70.

|| Annalen, 1918, 414, 283.

‡ J.C.S. 1937, p. 239.

§ Treibs, Ber. 1933, 66, 1488.

which on treatment with alkali yields *dl*- or *l*-2-isopropylhexan-5-one carboxylic acid (XIX), the probable mechanism involved in the formation of this acid being that set out in the scheme given below.



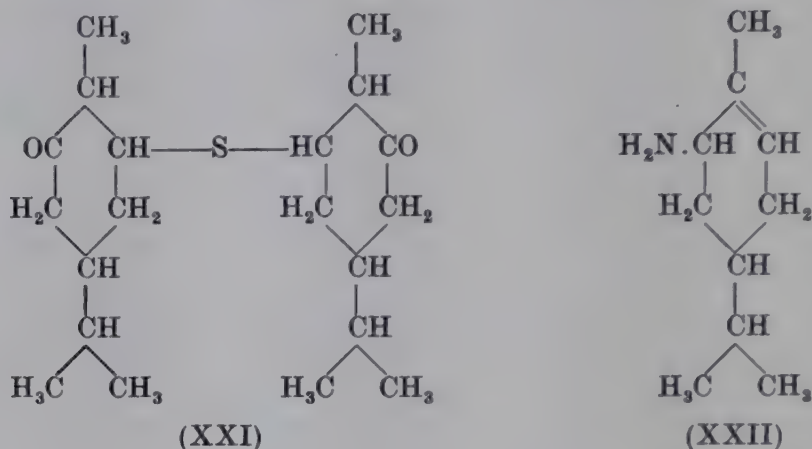
The *l*-ketonic acid is an oil, b.p. 220–240°/3 mm. (*semicarbazone*, m.p. 158–159°), whilst the *dl*-acid has m.p. 39–40° (*semicarbazones*, m.p. 137–138° and 151–152°). The constitution of the ketonic acid was confirmed by its oxidation with sodium hypobromite to β -isopropyladipic acid (XX).

According to Harries and Stirr,* carvotanacetone reacts very slowly with hydrogen bromide yielding an additive compound, C₁₀H₁₇OBr, from which the parent ketone can be regenerated. It dissolves readily in a neutral solution of sodium sulphite, from which it can be recovered by treatment with alkali; a method of purification used by Simonsen and Rau† for its separation from *l*-carvomenthone. Like carvone, it yields with

* *Loc. cit.*

† *J.C.S.* 1922, 121, 876.

hydrogen sulphide a characteristic derivative. Although this substance was described by Semmler,* it was first obtained in a state of purity by Harries and Stirr,† who found the *dl*-form to melt at 205° and the *d*-derivative at 222–225°. Some doubt exists as to the constitution of this substance and the most probable representation would appear to be (XXI).‡



With hydroxylamine, carvotanacetone reacts very readily to form a highly crystalline *oxime*; the *dl*-oxime melts at 92–93° and the *d*- and *l*-forms at 77°. Reduction of the *d*-oxime gives *d*-carvotanacetylamine (XXII), b.p. 93°/16.5 mm., $d_4^{15^\circ}$ 0.8917, $n_D^{15^\circ}$ 1.4815, $[\alpha]_D^{15^\circ}$ +190°, *acetyl* derivative, m.p. 112°.§ During the preparation of *d*-carvotanacetoxime from *d*-carvoxime, Wallach|| obtained evidence of the existence of a labile *oxime*, m.p. 66–67°, but the conditions for its preparation do not appear to be well defined. When the ketone is treated with an excess of hydroxylamine, a *hydroxylamino-oxime* is formed which crystallises with half a molecule of water of crystallisation. The *dl*-form melts at 162° and the *d*-form at 95–96°. The *phenylhydrazone* of *d*-carvotanacetone, m.p. 91–92°, was described by Simonsen and Rau.¶ It appears to be dimorphic but, owing to its instability, it is not suitable for the characterisation of the ketone. *d*-Carvotanacetone-2:4-dinitrophenylhydrazone has m.p. 191–192°. **

* *Ber.* 1894, 27, 895; 1900, 33, 2454.

† *Ibid.* 1901, 34, 1930.

‡ Challenger, Smith and Paton, *J.C.S.* 1923, 123, 1047.

§ Read and Swann, *J.C.S.* 1937, p. 239.

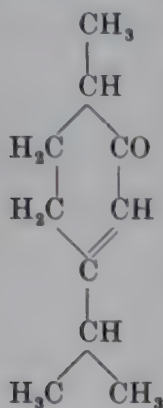
|| *Annalen*, 1914, 403, 74.

¶ *Loc. cit.*

** Short and Read, *J.C.S.* 1939, p. 1044.

CARVENONE

(Δ^3 -p-Menthen-2-one or
1-Methyl-4-isopropyl- Δ^3 -cyclohexen-2-one)



Although the ketone, carvenone, $C_{10}H_{16}O$ * has not been found to occur in nature, yet in view of its relationship to other plant products a consideration of its chemistry is desirable.

Carvenone was first obtained by Delalande† by the action of concentrated sulphuric acid on camphor at 200° . Sulphuric acid and other dehydrating agents react with camphor to give a complex mixture, which has been the subject of repeated study,‡ but it remained for Brecht, Rochussen and Mohnheim§ to show that the so-called “camphrene” was identical with carvenone.

In 1893 Wallach|| showed that when the glycerol, p-menthane-1:2:8-triol, obtained by the oxidation of α -terpineol (compare p. 259) was digested with dilute sulphuric acid, a substance, $C_{10}H_{16}O$, b.p. $231-233^\circ$, was formed. This was at first considered to be an alcohol, carveol, but two years later Wallach¶ prepared the same substance by the isomerisation of dihydrocarvone and recognised that it was a ketone. The suggestion that “carveol” was an unsaturated ketone and not an alcohol was, however, apparently first made by Wagner,** whilst at the same time Baeyer†† observed that it was formed by the action of sulphuric acid on carone.

* Carvenone has also been called *camphrene*, *camphenol*, *carveol* and *carvenol*.

† *L'Institut*, 1839, p. 399.

‡ *Inter al.* Chautard, *Compt. rend.* 1857, **44**, 66; Schwanert, *Annalen*, 1862, **123**, 298; Armstrong and Kipping, *J.C.S.* 1893, **63**, 75; Marsh and Gardner, *ibid.* 1897, **71**, 285; Marsh and Hartridge, *ibid.* 1898, **73**, 852.

§ *Annalen*, 1901, **314**, 374.

|| *Ibid.* 1893, **277**, 122.

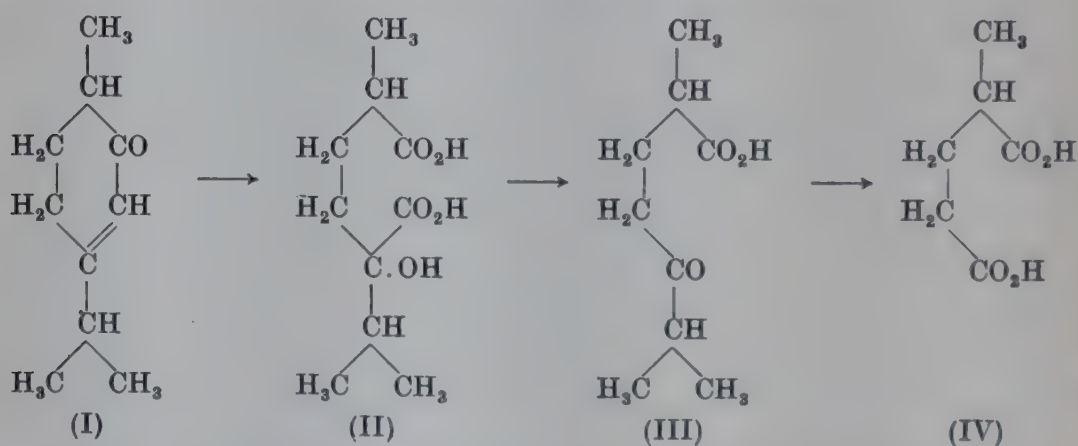
¶ *Ibid.* 1895, **286**, 130.

** *Ber.* 1894, **27**, 2273.

†† *Ibid.* p. 1920.

Wallach,* by the oxidation of the ketone with ferric chloride to carvacrol, established the relative positions of the methyl, isopropyl and carbonyl groups; the actual determination of its constitution and the proof that it was Δ^3 -p-menthen-2-one (I) was due, however, to Tiemann and Semmler,[†] although Baeyer[‡] had already suggested this formula.

By the oxidation of "camphrene" Armstrong and Kipping[§] had obtained α -methylglutaric acid (IV), yet, in view of the lack of homogeneity of their material, it was not possible to draw any conclusions regarding the constitution of the parent substance. Carvenone, on careful oxidation with potassium permanganate, was found by Tiemann and Semmler to give (i) a dibasic hydroxy acid, α -methyl- α' -isopropyl- α' -hydroxyadipic acid (II), m.p. 136–137°, (ii) α -methyl- γ -isobutyrylbutyric acid (III), b.p. 166–168°/14 mm., and (iii) α -methylglutaric acid (IV), m.p. 77–78°. The separation and identification of these acids left no doubt as to the constitution of carvenone.



The most suitable derivative for the characterisation of carvenone is the *hydroxylamino-oxime*, m.p. 167–168°, since although the *oxime*, m.p. 91–92°, can be readily prepared its melting-point lies very close to those of the oximes of carvone and dihydrocarvone.

Since carvenone contains an asymmetric carbon atom, it should exist in *d*-, *l*- and *dl*-forms, but it is doubtful if either of the optically active modifications has been prepared.^{||} This is

* *Annalen*, 1895, **286**, 134.

† *Ibid.* 1895, **28**, 1591.

‡ Compare Kondakov and Lutschinin, *J. pr. Chem.* 1899 [ii], **60**, 261.

§ *Ber.* 1898, **31**, 2889.

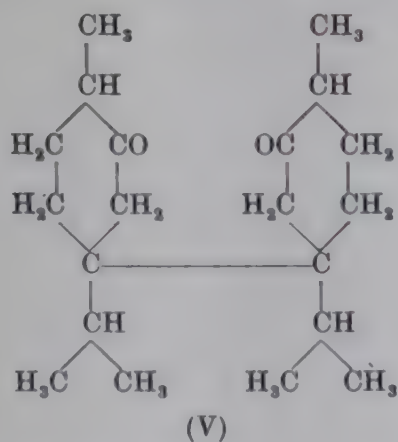
|| *J.C.S.* 1893, **68**, 97.

probably explained by the tendency for the ketone to enolise, a reaction which involves the asymmetric carbon atom and would thus cause racemisation. The isomeric ketone, piperitone, is also very readily racemised (compare p. 362).

Carvenone is a colourless oil with an odour resembling that of carvone. Auwers and Eisenlohr* gave the following constants for the ketone: b.p. 232–233°, d_4^{20} 0.9266, n_D^{20} 1.4824. It will be noticed that in addition to the marked exaltation in the molecular refraction (+1.04), due to the conjugation of the ethylenic linkage with the carbonyl group, the boiling-point is also very much higher than those of the isomeric menthenones. The calorific value has been determined by Roth and Östling,† whilst Crymble, Stewart, Wright and Rea‡ have shown that the ultra-violet absorption spectrum differed little from that of pulegone.

Carvenone can be prepared very readily by the isomerisation of dihydrocarvone (see p. 353); it is formed also when dihydrocarvone hydrobromide is heated with sodium acetate in acetic acid solution§ and by reduction of terpinene nitrosite with sodium and alcohol or with zinc dust and acetic acid.||

On reduction with sodium and alcohol, carvenone yields *carvomenthol*,¶ whilst with aluminium or sodium amalgam Harries and Kaiser** obtained a *pinacone*, b.p. 180–190°/10 mm., for which they suggested formula (V).



* *J. pr. Chem.* 1910 [ii], 82, 130.

† *Ber.* 1913, 46, 324.

‡ *J.C.S.* 1911, 99, 1265; see also Lowry and Lishmund, *ibid.* 1935, p. 1313.

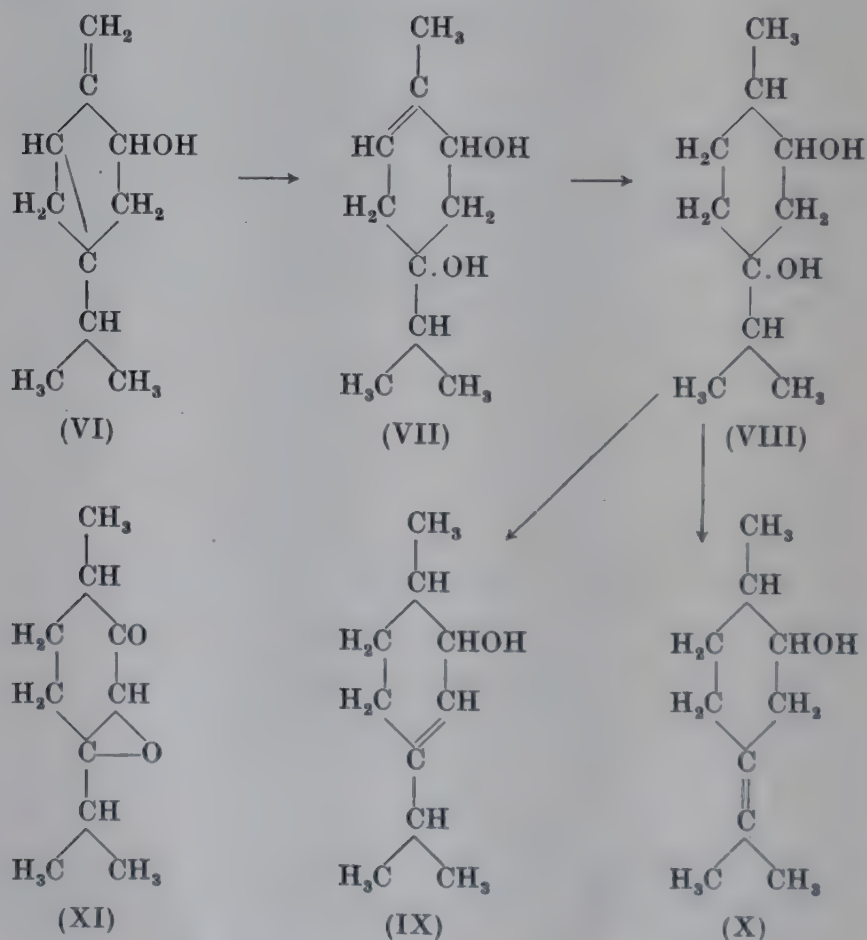
§ Baeyer, *Ber.* 1895, 28, 1592.

|| Wallach, *ibid.* 1907, 40, 580; *Annalen*, 1907, 356, 220; Harries and Majima, *Ber.* 1908, 41, 2516.

¶ Wallach, *Annalen*, 1893, 277, 130.

** *Ber.* 1899, 32, 1320.

Johnston and Read,* by the reduction of *dl*-carvenone with aluminium isopropoxide, obtained a crude *dl*-carvenol, b.p. 99–102°/14 mm., n_D^{17} 1.4799, from which they obtained a *p*-nitrobenzoate, m.p. 65° and a 3:5-dinitrobenzoate, m.p. 75–76°. This alcohol was also prepared indirectly by Wallach† from the dicyclic alcohol, *sabinol* (VI). On hydration with dilute sulphuric acid the unsaturated glycol, Δ^6 -*p*-menthene-2:4-diol (VII), is formed, which on catalytic hydrogenation is converted into *p*-menthane-2:4-diol (VIII), m.p. 93–94°. When this is digested with oxalic acid it yields a mixture of α -terpinene and carvenol (IX). The alcohol so obtained is probably not quite homogeneous, but contains a small quantity of the isomeric alcohol (X), since oxidation gives, in addition to carvenone, some acetone. The alcohol had the following constants: b.p. 219–221°, d^{22} 0.9250, n_D 1.4790.



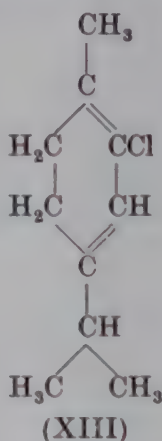
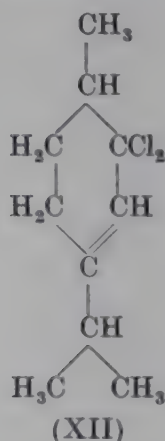
* *J.C.S.* 1934, p. 237.

† *Annalen*, 1917, 414, 203.

Reference has been made (p. 346) to the products formed on oxidation with potassium permanganate, whilst its conversion into diosphenol by the action of this reagent is dealt with on p. 416. The autoxidation of carvenone yields mainly the *oxide* (XI).*

With bromine, carvenone forms a liquid *dibromide* which on treatment with alkali yields carvacrol.[†] It does not appear to give any additive compounds with the halogen acids.

In the absence of any diluent, phosphorus pentachloride reacts with carvenone[‡] to yield 2-chloro-p-cymene; if, however, the reaction is carried out in ligroin,[§] a mixture of the *dichloride* (XII) and 2-chloro- $\Delta^{1:3}$ -p-menthadiene (XIII) is obtained.



With hydroxylamine, carvenone^{||} yields a mixture of the normal *oxime* and a *hydroxylamino-oxime*, which can be separated readily, since the oxime is volatile in steam. The oxime melts at 91–92°, a liquid oxime, which is formed simultaneously not having been characterised. The oxime was also prepared indirectly by Baeyer[¶] by the action of alkali on dihydrocarvoxime hydrobromide.

The hydroxylamino-oxime, m.p. 167–168° (XIV), gives on oxidation with mercuric oxide a blue nitroso-body (XV), which on warming with dilute mineral acids yields the normal oxime.

* Treibs, *Ber.* 1932, **65**, 163; 1933, **66**, 1484.

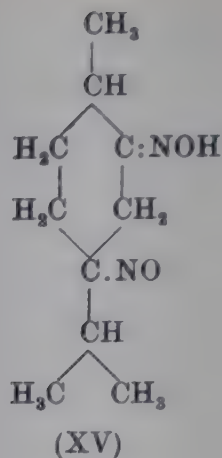
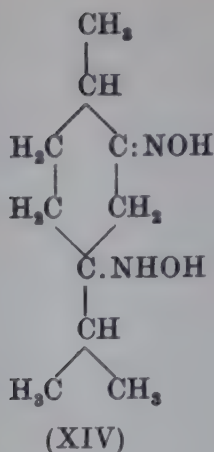
† Wallach, *Annalen*, 1894, **279**, 382; 1895, **286**, 128.

‡ Marsh and Hartridge, *J.C.S.* 1898, **73**, 854.

§ Klages and Kraith, *Ber.* 1899, **32**, 2559; Semmler, *ibid.* 1908, **41**, 4477; Wallach, *Annalen*, 1909, **368**, 15.

|| Wallach, *Ber.* 1895, **28**, 1963; *Annalen*, 1893, **277**, 126; 1907, **356**, 221; Bredt, Rochussen and Mohnheim, *ibid.* 1901, **314**, 379; Harries and Majima, *Ber.* 1908, **41**, 2521.

¶ *Ber.* 1894, **27**, 1921.

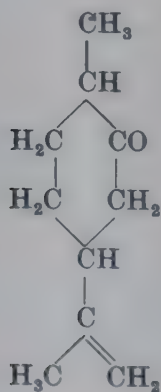


Two modifications of carvenone *semicarbazone** have been prepared, the α -form melting at $200\text{--}201^\circ$ and the more soluble β -form at $153\text{--}154^\circ$. The *hydrazone* is an oil, which according to Kishner† is converted into Δ^3 -*p*-menthene when it is distilled with potassium hydroxide.

In the presence of hydrogen chloride, carvenone condenses readily with two molecules of benzaldehyde to yield a substance $\text{C}_{24}\text{H}_{27}\text{O}_2\text{Cl}$, m.p. 197° , which on distillation loses hydrogen chloride with formation of a *dibenzylidene* derivative, $\text{C}_{24}\text{H}_{26}\text{O}_2$, m.p. $170\text{--}171^\circ$. The constitution of this substance has not been determined.

DIHYDROCARVONE

($\Delta^{8(9)}$ -*p*-Menthen-2-one or
1-Methyl-4-isopropenylcyclohexan-2-one)

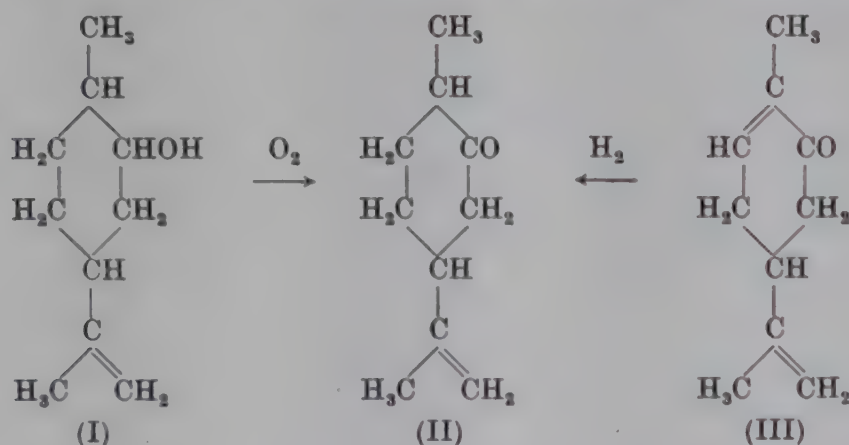


* Baeyer, *Ber.* 1894, **27**, 1923; 1895, **28**, 1592; Wallach, *ibid.* p. 1960.

† *J. Russ. Phys. Chem. Soc.* 1911, **43**, 951.

l-Dihydrocarvone, $C_{10}H_{16}O$, occurs in nature in oil of caraway (from the fruits of *Carum carui* L.) and it was first separated from this oil by Schimmel and Co. in 1905.* It had, however, been prepared and its constitution determined many years previously.

In 1893 Wallach[†] showed that *dihydrocarveol* (I) on oxidation with chromic acid gave the corresponding ketone, *dihydrocarvone* (II) and in the following year, in collaboration with Schrader,[‡] he described the preparation of *l*-dihydrocarvone by the reduction of *d*-carvone (III) with zinc dust in the presence of alkali. From its method of preparation (from dihydrocarveol), it appeared probable that the ketone was represented by the formula[§] (II) and this was confirmed by the contemporaneous



researches of Tiemann and Semmler^{||} and of Wallach.[¶] When the ketone is oxidised with potassium permanganate, it yields *p*-menthan-2-one-8:9-diol (IV), m.p. 115–120°, from which a *semicarbazone*, m.p. 187°, and an *oxime*, m.p. 202°, can be prepared. This glycol on further oxidation with chromic acid gives the *diketone* (V), b.p. 152–160°/22 mm. (*semicarbazone*, m.p. 203–204°). The formation of these derivatives is only explicable if dihydrocarvone, like the parent alcohol, dihydrocarveol, has the ethylenic linkage in the 8(9)-position.

* Schimmel's Report, 1905, Apr. p. 50.

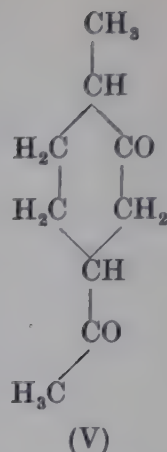
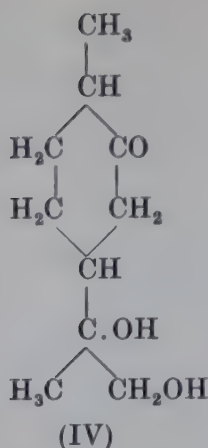
† Annalen, 1893, 275, 114.

‡ Ibid. 1894, 279, 377.

§ This formula was adopted in 1895 after Wagner (Ber. 1894, 27, 1652, 2271) had suggested the correct constitution for carvone (see p. 395). The formulae suggested previously for dihydrocarvone by Wallach and by Baeyer (ibid. 1895, 28, 1966) are now only of historic interest.

|| Ber. 1895, 28, 2141.

¶ Ibid. p. 2704.



Since dihydrocarvone contains two asymmetric carbon atoms, it should exist in two pairs of dextro- and laevo-rotatory forms as well as the two *dl*-forms. Only one dextro- and one laevo-form have been described together with the corresponding *dl*-form, but there is no evidence that these were optically pure. The ketone is a colourless oil with an odour reminiscent of both menthone and carvone. A specimen of the natural ketone had the following constants: b.p. $221^\circ/735.5$ mm., d^{15}_D 0.9297, n^{20}_D 1.4710, $[\alpha]_D -16.8^\circ$, whilst Wallach,* for a specimen prepared from *d*-carvone, found b.p. $221\text{--}222^\circ$, d^{19}_D 0.928, n^{19}_D 1.4717, $[\alpha]_D -17.7^\circ$. Very similar values have been quoted by Kondakov and Lutschinin† for the *d*-ketone. The heat of combustion has been determined by Roth and Östling,‡ whilst the ultra-violet absorption spectrum has been studied by Crymble, Stewart, Wright and Rea.§

Dihydrocarvone, which can be purified readily through the crystalline compound which it forms with sodium bisulphite, can be characterised by the preparation of its *oxime*, *d*- and *l*-forms, m.p. $88\text{--}89^\circ$, *dl*-, m.p. $115\text{--}116^\circ$.

In addition to the methods referred to above, *dl*-dihydrocarvone has been prepared in an interesting manner from *nitrosopinene* (VII), which is formed when *pinene nitrosochloride* (VI) is treated with sodium ethoxide." With bromine, nitrosopinene gives a *dibromide* (VIII) from which, by reduction with zinc dust, *dl*-dihydrocarvone can be obtained.

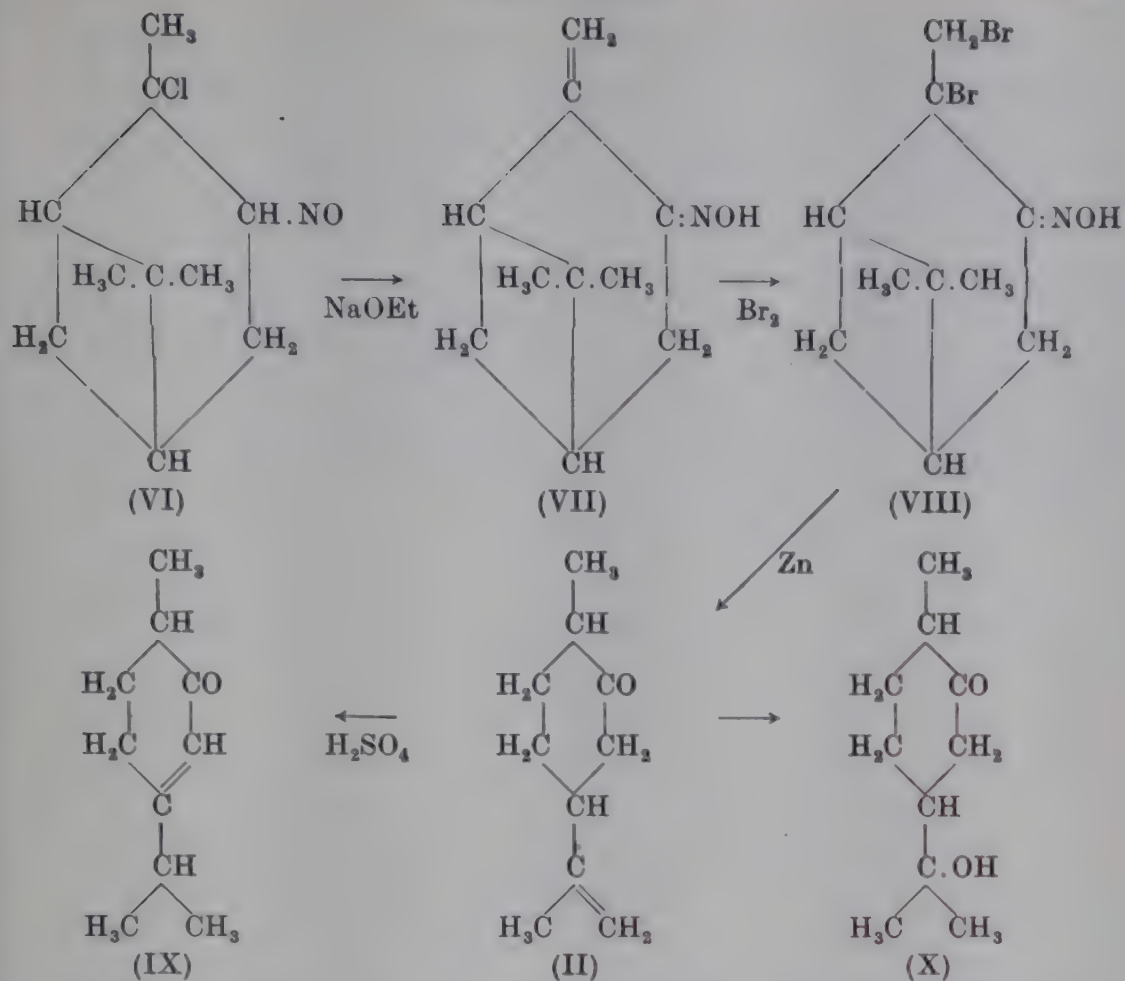
* *Annalen*, 1893, 275, 116.

† *J. pr. Chem.* 1899 [ii], 60, 261.

‡ *Ber.* 1913, 46, 324; compare Swietoslawski, *J. Amer. Chem. Soc.* 1920, 42, 1098.

§ *J.C.S.* 1911, 99, 1265.

|| Wallach, *Annalen*, 1898, 300, 290; 1900, 313, 368.



Dihydrocarvone can be obtained also by the electrolytic reduction of carvone* or carvoxime.†

The ethylenic linkage in dihydrocarvone is somewhat labile and it shows a tendency to pass into the ring with the formation of the isomeric ketone, *carvenone* (IX). This isomerisation was observed by Wallach‡ to occur when the ketone was heated to a high temperature or on digestion with dilute sulphuric acid, whilst Baeyer§ showed that the same change took place on treatment with concentrated sulphuric acid. Isomerisation to carvenone can also be brought about by the action of formic acid|| or by hydrochloric acid at $120\text{--}130^\circ$.¶ It is possible that the isomerisation takes place with the intermediate formation of *p-menthan-2-on-8-ol* (X), since Rupe and Liechtenhan** found that this alcohol could be prepared by the action of sulphuric acid

* Law, *J.C.S.* 1912, **101**, 1549.

† Rupe and Löffel, *Ber.* 1914, **47**, 2151.

‡ *Ber.* 1894, **27**, 1921.

§ Müller, *J. pr. Chem.* 1916 [ii], **93**, 21.

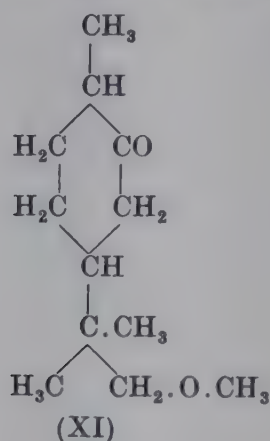
|| *Annalen*, 1895, **286**, 131.

¶ Klages, *ibid.* 1899, **32**, 1519.

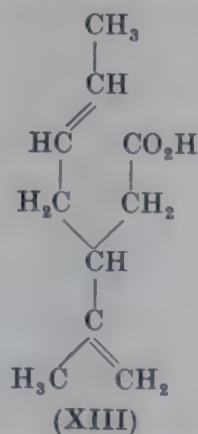
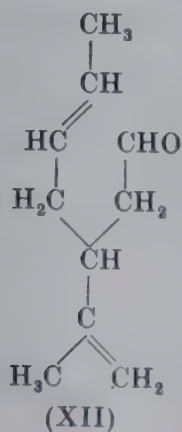
** *Ber.* 1906, **39**, 1124.

(40 per cent.) on the ketone. The *semicarbazone** of this alcohol melts at 176°, and it is interesting to note that it is obtained also when α -terpineol nitrosochloride is heated with semicarbazide hydrochloride.† On reduction with sodium and alcohol or with aluminium isopropoxide‡ dihydrocarvone yields dihydrocarveol.

Treibs§ has shown that dihydrocarvone undergoes an unusual reaction with acid methanol to give (XI). Carvone behaves in a similar manner (see p. 404), but carvotanacetone is unaffected by this treatment, which appears to indicate that the reaction applies only to the exocyclic type of ethylenic linkage.



The action of sunlight on the ketone was investigated by Ciamician and Silber,|| who obtained as the main products of the reaction an *aldehyde*, which they considered to have the formula (XII) and the related *acid* (XIII) but no rigid proof of the constitution of these two substances has been furnished.



* Rupe and Schlochoff, *Ber.* 1905, **38**, 1719; Knoevenagel and Samel, *ibid.* 1906, **39**, 677.

† Rupe and Altenburg, *Ber.* 1910, **43**, 3473.

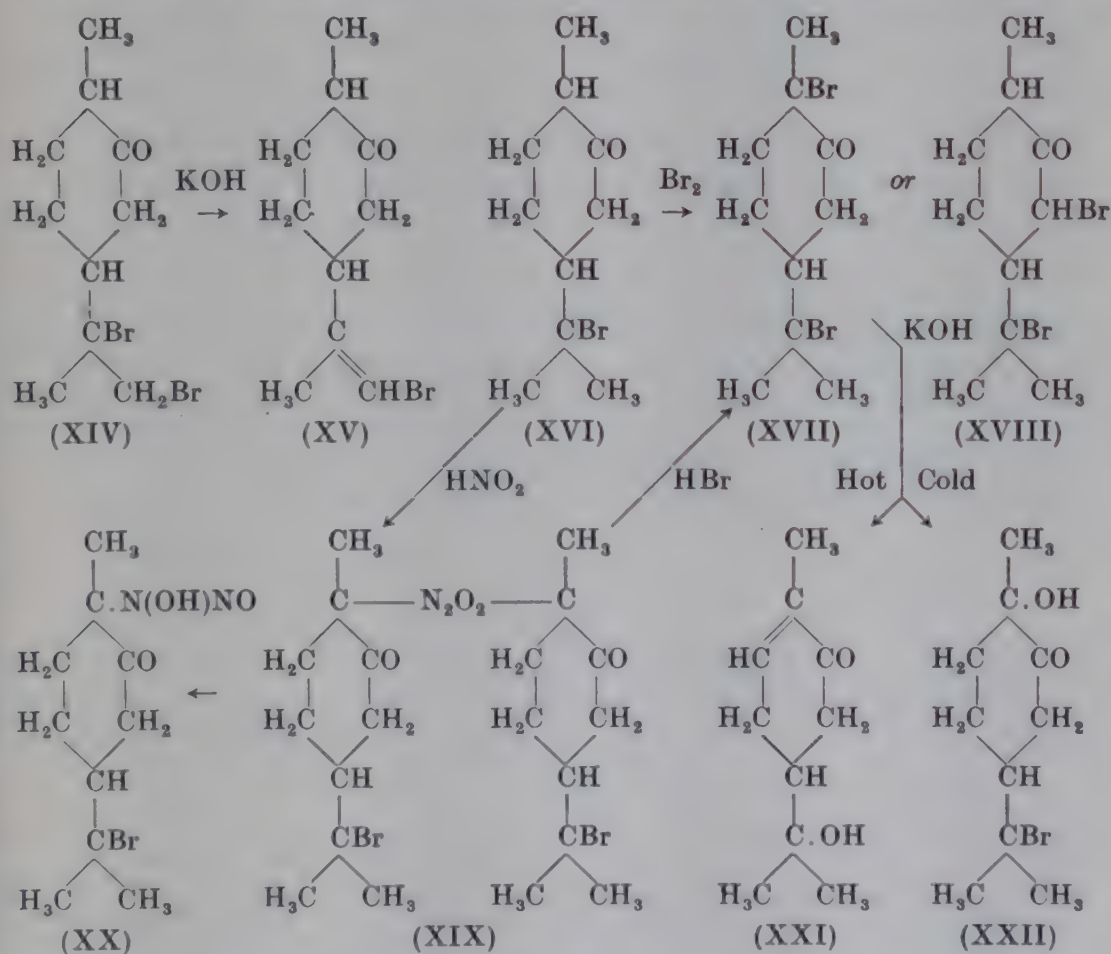
‡ Johnston and Read, *J.C.S.* 1934, p. 237.

§ *Ber.* 1937, **70**, 387.

|| *Ibid.* 1908, **41**, 1928.

Oxidation of dihydrocarvone with ferric chloride in acetic acid solution yields carvacrol,* whilst the products of the oxidation with potassium permanganate have been discussed on p. 351. Carvacrol is also formed when the ketone is dehydrogenated with palladium.†

The halogen derivatives of the ketone have been studied by Wallach‡ and also by Baeyer.§ The action of bromine in acetic acid gives a liquid *dibromide* which is undoubtedly represented by (XIV), addition taking place at the ethylenic linkage. This dibromide reacts readily with alkali with the formation of carvacrol and carvenone, but the main product of the reaction is a liquid *monobromide*, which decomposes on distillation but on reduction with sodium and alcohol yields dihydrocarveol. There can be little doubt therefore that it is represented by



* Wallach, *Annalen*, 1895, 286, 134.

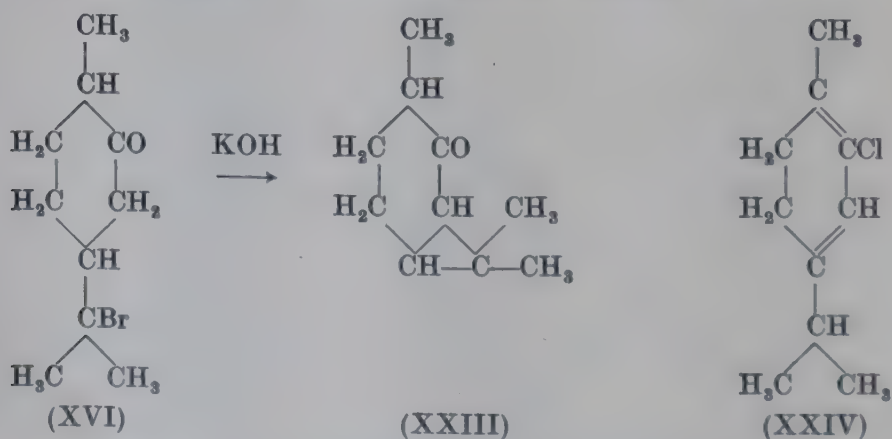
† Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

‡ *Annalen*, 1894, 279, 389; 1895, 286, 127; 1918, 414, 277.

§ *Ber.* 1895, 28, 1594.

formula (XV). When dihydrocarvone is dissolved in acetic acid containing hydrogen bromide a liquid *hydrobromide* (XVI) is obtained which, on bromination, gives a crystalline *dibromide* (*l*-, m.p. 69–70°, *dl*-, m.p. 96–97°). From its method of preparation, it is obvious that there are two possible formulae (XVII) and (XVIII), but there is no doubt that (XVII) is the correct representation for the following reasons. It was observed by Baeyer that when dihydrocarvone hydrobromide (XVI) was treated with ethyl nitrite and acetyl chloride, a *bis-nitroso-derivative* (XIX) was formed. This substance reacted with hydrogen bromide to give a mixture of a dibromide (XVII) and a *nitrosylic acid* (XX), the former being identical with that obtained by the bromination of the hydrobromide. Support for this constitution for the dibromide is furnished by a study of its reaction with alkali; when it is digested with dilute alkali it yields an unsaturated *hydroxy-ketone* (XXI), which is converted into carvacrol by the action of sulphuric acid; if however an ethereal solution of the bromide is shaken with sodium hydroxide (40 per cent.) it gives, according to Baeyer,* the *bromohydroxyketone* (XXII).

Dihydrocarvone hydrochloride and *hydrobromide* (XVI), which can be prepared very readily by the treatment of an acetic acid solution of the ketone with the appropriate halogen acid, are oils, which distil without decomposition under diminished pressure. Both the active and inactive modifications have been prepared, and, on treatment with alkali, were shown by Baeyer† to give the interesting dicyclic ketone *carone* (XXIII).

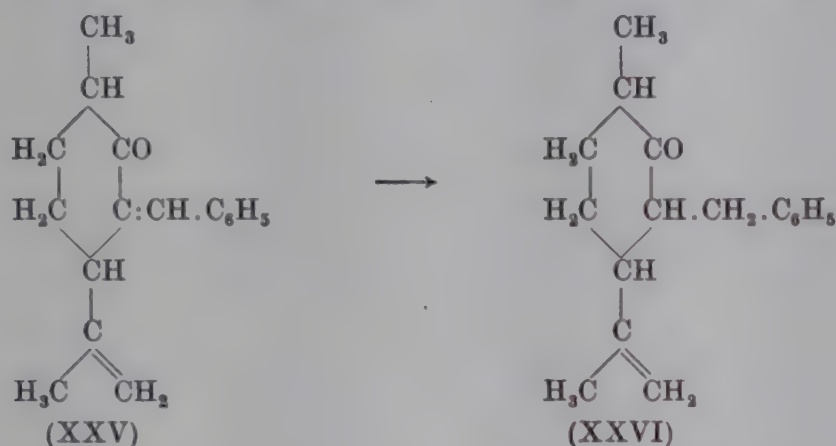


* *Ber.* 1898, 31, 3211.

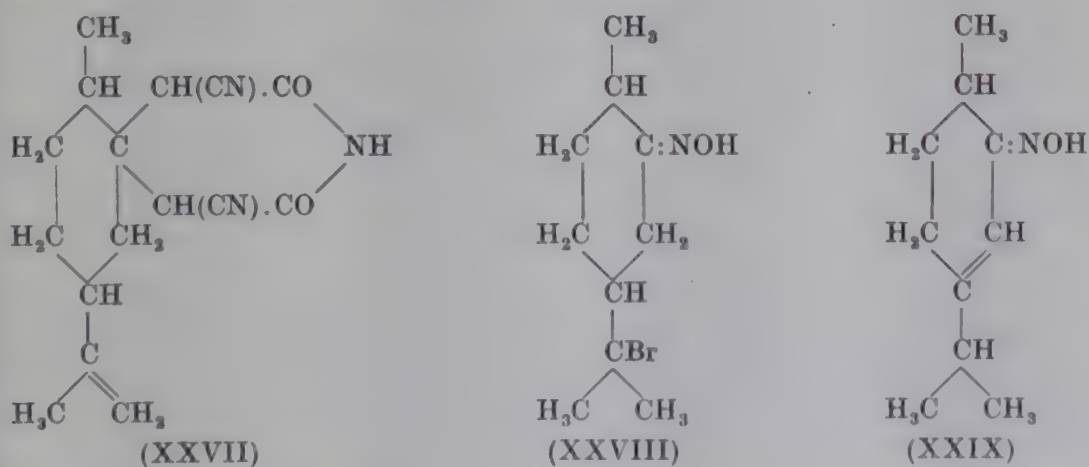
† *Ibid.* 1894, 27, 1915; compare Kondakov and Gorbunov, *J. pr. Chem.* 1897 [ii], 56, 256; Müller, *ibid.* 1916 [ii], 93, 21.

Klages and Kraith* have found that dihydrocarvone reacts with phosphorus pentachloride to give 2-chloro- $\Delta^{1:3}$ -p-menthadiene (XXIV), the parent ketone being isomerised to carvenone during the course of the reaction.

Benzylidenedihydrocarvone (XXV) was prepared by Wallach† by the action of benzaldehyde on the ketone in the presence of alkali. It is an oil, b.p. 187–190°/10 mm. (oxime, m.p. 145–146°). Reduction of this derivative gives benzylidihydrocarveol (XXVI), b.p. 182–184°/11 mm. (phenylurethane, m.p. 233–234°).



The condensation of ethyl cyanoacetate and dihydrocarvone has been investigated by Kon and Thorpe,‡ who showed that the ω -imide of $\alpha\alpha'$ -dicyano-2-methyl-5-isopropenylcyclohexane-1:1-diacetic acid (XXVII) was formed. Unfortunately they were unable to hydrolyse this substance.



* Ber. 1899, 32, 2560.

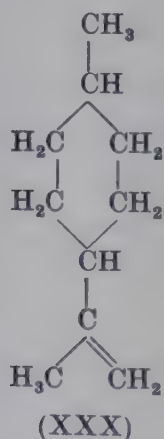
† Annalen, 1899, 305, 268; compare Müller, Ber. 1921, 54, 1479.

‡ J.C.S. 1919, 115, 692.

As was mentioned on p. 352 the *dihydrocarvoximes* are readily prepared and are eminently suitable for the characterisation of the ketone. The optically active oximes show dimorphism, crystallising both in needles and prisms, the latter being the stable modification. By treatment with hydrogen bromide a crystalline *hydrobromide*, m.p. 109° , is obtained, which must be represented by formula (XXVIII) and is therefore a derivative of bromocarvomenthone. When dihydrocarvoxime is dissolved in concentrated sulphuric acid an isomeric *oxime*, m.p. $87-88^{\circ}$, is formed, which does not yield a crystalline hydrobromide. The constitution of this *iso-oxime* has not been determined, but it very probably is *carvenoneoxime* (XXIX), since, as mentioned previously (p. 353), concentrated sulphuric acid readily isomerises dihydrocarvone to carvenone.

dl-Dihydrocarvone *semicarbazone* was prepared by Baeyer* and melts at $187-188^{\circ}$, the optically active form melting at $189-191^{\circ}$.†

The *hydrazone* is an oil, which decomposes on distillation, but which, when heated with sodium ethoxide to $180-190^{\circ}$ under pressure, is converted into *dihydrolimonene* (XXX), b.p. $168-169^{\circ}$, d_{16}^{21} 0.8217, n_D 1.4561.



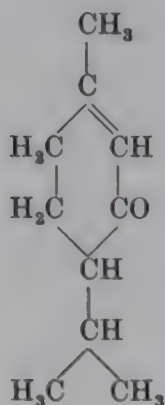
Mention has been made already (p. 164) of the triazo derivatives of the ketone, which can be obtained by the action of oxalic acid on dipentene and *d*- and *l*-limonene nitrosoazides.

* Ber. 1894, 27, 1923.

† Wallach, *ibid.* 1895, 28, 1960.

PIPERITONE

(Δ^1 -p-Menthen-3-one or
1-Methyl-4-isopropyl- Δ^1 -cyclohexen-3-one)



Although the chemistry of the interesting ketone known as piperitone has only been studied in recent years, its occurrence may be considered to have been observed originally in 1788, when Dr White, Surgeon-General to the new settlement of New South Wales, gave the name "Peppermint Tree" to a species of *Eucalyptus*, from the leaves of which an oil could be obtained resembling in smell the peppermint oil from *Mentha piperita*. This *Eucalyptus*, now known as *E. piperita*, occurs in the Sydney district and the Blue Mountain Ranges of New South Wales.

Prior to 1900, no attempt was apparently made to determine the nature of the odoriferous principle of the oil, although it had been suggested that it was due to menthone.* In this year Smith† isolated from the oil of *E. dives* a ketone, to which he erroneously gave the formula, $C_{10}H_{18}O$, and some years later Baker and Smith gave to it the name piperitone.‡ Piperitone was subsequently found to occur in a very large number of *Eucalyptus* oils, and, in the case of certain varieties of *E. dives* constitutes as much as 40 per cent. of the distillate.§ It was not until 1920 that experiments on the constitution of piperitone commenced. In this year Smith and Penfold|| showed piperitone

* Schimmel's Report, 1888, April, p. 20.

† J. Proc. Roy. Soc. New South Wales, 1900, 34, p. xxxiv.

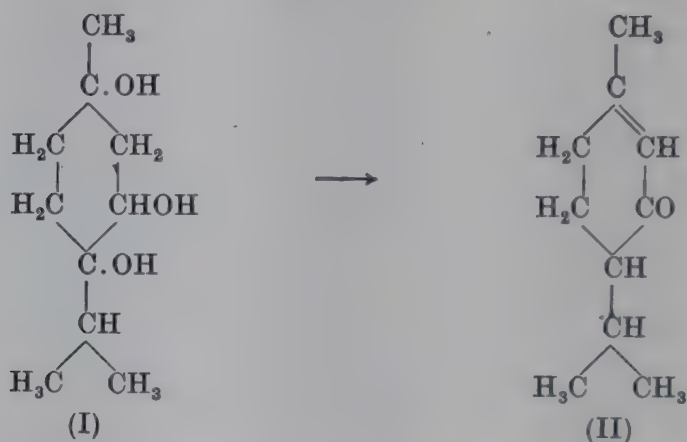
‡ A Research on the Eucalypts, 1st ed., 1902, p. 229.

§ Compare Read, Smith and Bentivoglio, J.C.S. 1922, 121, 584 footnote.

|| J. Proc. Roy. Soc. New South Wales, 1920, 54, 40.

to be an unsaturated ketone, $C_{10}H_{16}O$, which, when purified through its bisulphite compound, was optically inactive ($[\alpha]_D - 1^\circ$), but if purified by fractional distillation under diminished pressure, was markedly laevorotatory ($[\alpha]_D - 42.8^\circ$). Smith and Penfold showed further that it must be a *p*-menthen-3-one, since it gave *thymol* on oxidation with ferric chloride and *menthone* on reduction with hydrogen, using a nickel catalyst. The position of the ethylenic linkage remained undetermined.

In 1908 Wallach and Meister* obtained dl- Δ^1 -*p*-menthen-3-one (II) from the glycerol, *p*-menthane-1:3:4-triol (I) by distillation with dilute mineral acids, and they characterised it by the preparation of a very sparingly soluble *semicarbazone*, m.p. 224–226°. Shortly afterwards, the dextrorotatory form of this ketone



was isolated from Japanese peppermint oil (from *Mentha arvensis* var. *piperascens*),[†] and in 1915 Roberts[‡] showed that the oil from the Sudan “Mahareb” grass, *Cymbopogon sennarensis* Chiov., contained approximately 45 per cent. of this ketone. Both these ketones were fully characterised (i) by the preparation of the *semicarbazone*, shown to exist in two forms, α -form, m.p. 224–226°, identical with that described by Wallach and Meister, and a more soluble β -form, m.p. 171–172°, (ii) an *oxime*, m.p. 107–109°, and (iii) a *hydroxylamino-oxime*, m.p. 164–165°. Oxidation of the ketone with potassium permanganate led to the formation of products which will be described below, and which left no doubt as to the position of the ethylenic linkage.

* *Annalen*, 1908, **362**, 272.

† *Schimmel's Report*, 1910, Oct. p. 97.

‡ *J.C.S.* 1915, **107**, 1466.

In 1921 Read and Smith* published a detailed account of a renewed study of the properties of piperitone from *E. dives*. They did not regard it as identical with Δ^1 -*p*-menthen-3-one, although they prepared from it a semicarbazone, m.p. 219–220°, an oxime, m.p. 110–111° and a hydroxylamino-oxime, m.p. 169–170°, and they remarked on the close agreement of the melting-point of their semicarbazone with that described by Wallach and Meister. They were probably influenced in coming to this erroneous conclusion by their important observation that piperitone gave a highly characteristic *benzylidene* derivative, m.p. 61°, indicating apparently the presence of the grouping $\text{—CH}_2\text{—CO—}$.

In the same year Simonsen† isolated from the oil of *Andropogon Jwarancusa* Jones, a grass closely related to *C. sennarensis* Chiov., a ketone, which agreed in all its properties with the piperitone of Read and Smith except that it was strongly dextro-rotatory ($[\alpha]_D + 37.6^\circ$). From his ketone Simonsen prepared an α -semicarbazone, m.p. 224–226°, a β -semicarbazone, m.p. 174–176°, an oxime, m.p. 117–118°, a hydroxylamino-oxime, m.p. 170–171°, and a benzylidene derivative, m.p. 61°. After confirming the identity of his ketone with Δ^1 -*p*-menthen-3-one by degradative oxidation, he concluded that there could be little doubt that this constitution must also be given to the *l*-piperitone from *E. dives*, and he suggested an explanation (see below) to account for the formation of the benzylidene derivative.

The identity of *l*-piperitone with Δ^1 -*p*-menthen-3-one was proved simultaneously by Penfold,‡ who examined the products formed on oxidation of the ketone with potassium permanganate. The subsequent thorough investigations of Read and his collaborators have fully substantiated this view.

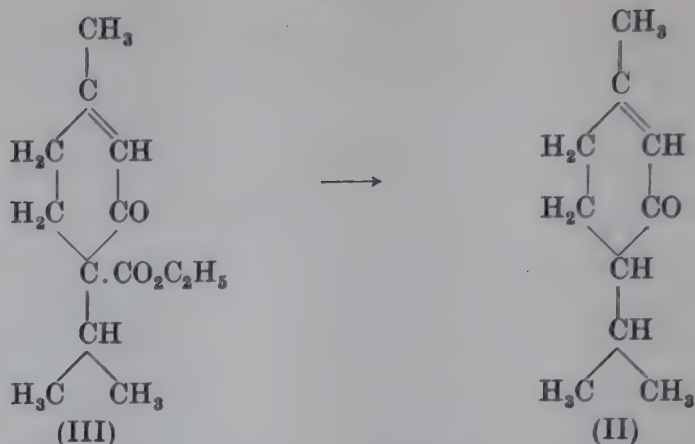
A synthesis of *dl*-piperitone has been described by Walker,§ who condensed ethyl α -isopropylacetoacetate with β -chloroethyl methyl ketone and obtained *ethyl* Δ^1 -*p*-menthen-3-one-4-carboxylate (III). Removal of the carbethoxy group by alkaline hydrolysis gave a ketone, b.p. 107–109°/12 mm., $n_D^{15} 1.4854$, which was identified as *dl*-piperitone (II) by the formation of the oxime, m.p. 117°.

* *J.C.S.* 1921, 119, 779.

† *Ibid.* p. 1646.

‡ *J. Proc. Roy. Soc. New South Wales*, 1921, 55, 139; *Perfum. essent. Oil Rec.* 1922, 13, 322.

§ *J.C.S.* 1935, p. 1585.



Piperitone has also been obtained* by hydrogenation of diosphenol (p. 418) and by the reduction of 5-methyl-2-*iso*-propylanisole with sodium and liquid ammonia.†

Piperitone is a pleasant camphoraceous smelling oil, which although colourless when freshly distilled, becomes yellow on keeping, this tendency being, however, much less marked in specimens purified through the semicarbazone.‡ For the very carefully purified ketone the following constants have been observed by Read and Smith:§ *d*-piperitone (from *A. Jwarancusa*), b.p. 116–118.5°/20 mm., $d_4^{20^\circ}$ 0.9344, $n_D^{20^\circ}$ 1.4848, $[\alpha]_D^{20^\circ} + 49.13^\circ$; *l*-piperitone (from *E. dives*), b.p. 109–110.5°/15 mm., $d_4^{20^\circ}$ 0.9324, $n_D^{20^\circ}$ 1.4848, $[\alpha]_D^{20^\circ} - 51.53^\circ$; *dl*-piperitone (from *E. dives*), b.p. 232–233°/768.6 mm., 113°/18 mm., $d_4^{20^\circ}$ 0.9331, $n_D^{20^\circ}$ 1.4845, $[\alpha]_D \pm 0^\circ$. According to Huggett,|| however, the *l*-piperitone in *E. dives* is not entirely free from the *dl*-ketone, and by a process of fractional crystallisation at -50° ¶ he has obtained *l*-piperitone with $[\alpha]_D^{20^\circ} - 67.8^\circ$, though the other physical constants do not differ appreciably from those recorded by Read and Smith.

The absorption spectrum of the ketone has been studied by several workers.**

As mentioned above, the ease with which *l*-piperitone racemises was first observed by Smith and Penfold†† and this property has

* Walker and Read, *J.C.S.* 1934, p. 238.

† Birch, *ibid.* 1944, p. 432.

‡ Read and Smith, *ibid.* 1922, 121, 1872.

§ *Ibid.* 1923, 123, 2268.

|| *J.S.C.I.* 1941, 60, 67.

¶ *B.P.* 508001.

** Lowry and Lishmund, *J.C.S.* 1935, p. 1313; Cooke and Macbeth, *ibid.* 1938, p. 1408; Gillam, Lynas-Gray, Penfold and Simonsen, *ibid.* 1941, p. 60; Mohler and Lohr, *Helv. Chim. Acta*, 1937, 20, 1183; Naves and Papazian, *ibid.* 1942, 25, 1023, 1046.

†† *J. Proc. Roy. Soc. New South Wales*, 1920, 54, 40.

been carefully studied by Read and Smith.* When distilled at the ordinary pressure *l*-piperitone is partially racemised and almost complete racemisation is observed when the ketone is purified through the compound which it forms with sodium bisulphite. This change probably takes place during the regeneration of the ketone with alkali, since Read and Smith found that digestion with an alcoholic solution of potassium hydroxide caused complete racemisation, a change effected even more advantageously with sodium ethoxide. The racemisation is probably due to enolisation of the ketone, which involves a loss of the original molecular asymmetry. Acids are much less effective in causing racemisation, and the active ketone can be recovered unchanged after solution in 90 per cent. sulphuric acid, although it is almost completely racemised by an aqueous solution of sulphur dioxide at the ordinary temperature.

In view of its technical importance, the most satisfactory methods for the separation, detection and estimation of piperitone have been carefully studied. The former has been investigated by Read and Smith,† who find that by fractional distillation a ketone of 93 per cent. purity can be obtained; it can, however, best be obtained in a high state of purity by the preparation of the crystalline derivatives which it forms on treatment with sodium bisulphite or sodium sulphite. According to Penfold‡ piperitone can be most conveniently detected by taking advantage of the fact that when an alcoholic-ethereal solution of the ketone is reduced with sodium amalgam, a *pinacone*, $C_{20}H_{34}O_2$, is produced which melts at 142–149° (see below).

The bromination of piperitone in acetic acid solution was investigated by Wallach and Hallstein,§ who found that a liquid *dibromide* (IV) was formed, which, on treatment with dilute alkali (2 per cent.), gave a crystalline *monobromide*, m.p. 42–43°, the constitution of which was not determined. Oxidation of the monobromide led to the formation of a *keto-acid*, $C_{10}H_{14}O_3$, m.p. 105–106°, and oxalic acid, whilst bromination gave a dibromothymol, m.p. 76°. In a later investigation, Davies and Simonsen|| proved the monobromide to be (V) by oxidation with potassium

* *Loc. cit.* p. 2270.

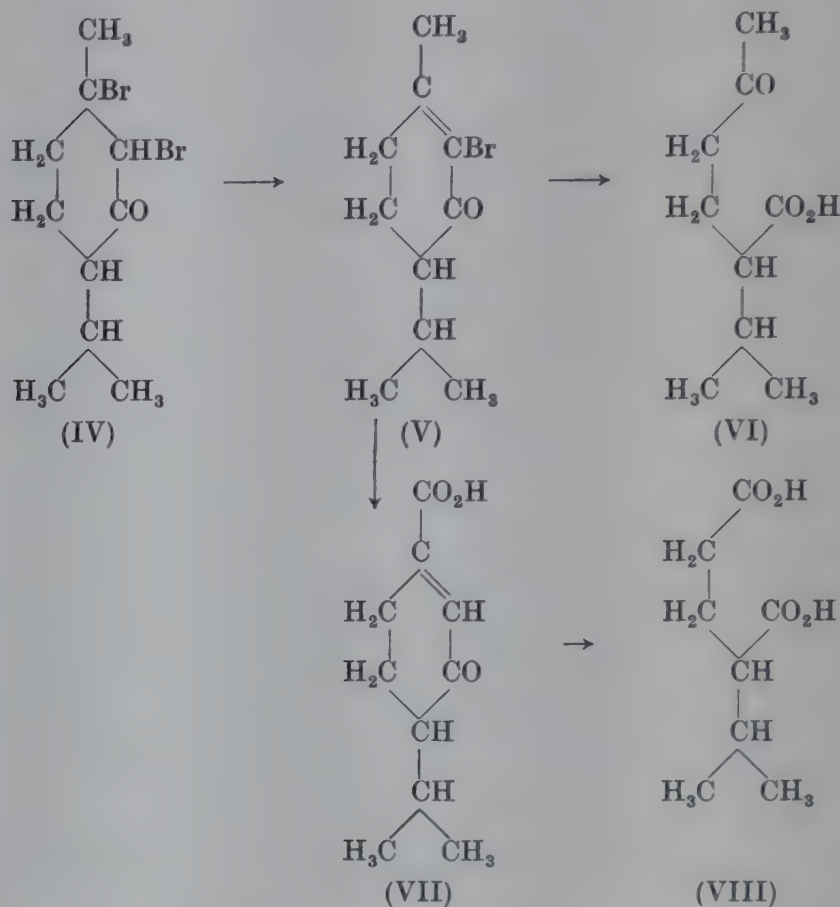
† *J.S.C.I.* 1923, 42, 339 T.

‡ Technological Museum, Sydney, *Bulletin*, No. 1.

§ *Annalen*, 1918, 414, 287.

|| *J.C.S.* 1932, p. 1422.

permanganate, when γ -acetyl- α -isopropylbutyric acid (VI) was formed. They showed also that the keto-acid was 4-isopropyl- Δ^1 -cyclohexen-3-one-1-carboxylic acid (VII), since on further oxidation it gave α -isopropylglutaric acid (VIII).



With hypochlorous acid *dl*-piperitone gives a crystalline *chlorohydrin*, m.p. 101–102°.*

The reduction of piperitone under a variety of conditions has been studied in great detail. Smith and Penfold,[†] who would appear to have been the first to investigate the reduction, found that when the ketone was reduced by the Sabatier-Senderens process, using a nickel catalyst at 175–180°, a menthone was formed in almost quantitative yield. The menthone, which was slightly optically active ($[\alpha]_D -0.15^\circ$), gave an oxime, m.p. 80°, and two semicarbazones, m.p. 187–188° and 156° respectively. These authors also investigated the reduction of the ketone with

* *J.C.S.* 1929, p. 2075.

† *J. Proc. Roy. Soc. New South Wales*, 1920, 54, 40.

sodium amalgam, when, as in the case of carvone, a pinacone, $C_{20}H_{34}O_2$, is formed. This ketone melts somewhat indefinitely at $142-149^\circ$ and by fractional crystallisation may be separated into isomerides melting respectively at $135-136^\circ$ and $166-167^\circ$.^{*} This pinacone is formed also when the reduction is carried out with sodium in aqueous ethereal solution, but, at the same time, some menthol is produced.

A systematic study of the reduction of *d*-, *l*- and *dl*-piperitones has been carried out by Read and his collaborators.[†] These researches, which have done so much to clarify the chemistry of the isomeric menthones and menthols, have been already considered (pp. 239-241) and need only be referred to briefly here.

Reduction of either *d*-, *l*- or *dl*-piperitone with sodium in alcoholic solution yields *dl*-isomenthols and *dl*-menthols, some *dl*- α -phellandrene being formed simultaneously.

The catalytic hydrogenation of both optically active and racemic forms of the ketone was studied by Read, and, more recently, by Hückel.[‡] With a palladium catalyst *dl*-piperitone gives *dl*-isomenthone and a little *dl*-menthone, whilst from the optically active ketones the corresponding optically active *iso*-menthones were prepared. No reduction of the carbonyl group was observed when a pressure of 20 atmospheres was employed. With a nickel catalyst at 180° , *dl*-isomenthone in a yield of 70 per cent. was the main product of the reaction. It is important to note, however, that in every case the hydrogenation is accompanied by dehydrogenation and formation of thymol, which may be obtained in a yield varying between 10 and 60 per cent., the yield being apparently greater the less pure the piperitone.[§] The reduction of *l*-piperitone with aluminium isopropoxide gives *l*-piperitol (p. 288).^{||}

Preliminary experiments on the electrolytic reduction of *l*-piperitone in 10 per cent. sulphuric acid solution with a platinum anode and an activated nickel cathode were made by

* Compare Read, *Chemical Reviews*, 1930, 7, 13.

† *J.C.S.* 1923, 123, 2916; 1925, 127, 2782; 1926, pp. 2209, 2223; 1929, p. 2068; compare Treibs and Schmidt, *Ber.* 1927, 60, 2335.

‡ Hückel and Niggemeyer, *Ber.* 1939, 72, 1354; Hückel and Wagner, *ibid.* 1941, 74, 657.

§ *J.C.S.* 1923, 123, 2916; 1925, 127, 2782; 1926, pp. 2209, 2223; 1929, p. 2068; compare Treibs and Schmidt, *Ber.* 1927, 60, 2335.

|| Read and Walker, *J.C.S.* 1934, p. 308.

Penfold and Morrison,* who obtained an *isomenthone* in a yield of 90 per cent. Hughesdon, Smith and Read,[†] who worked with lead electrodes, the cathode liquid being a dilute alcoholic solution of sodium acetate and the anode a sodium carbonate solution, obtained mainly the *pinacone* with very little *menthone*. They also reported a similar result using a solution of sulphuric acid with a zinc cathode.

As has been mentioned already (p. 360), Smith and Penfold showed that *piperitone* gave, on oxidation with ferric chloride, *thymol* in a yield of approximately 25 per cent. *Thymol* is also formed when the ketone is oxidised with selenium dioxide[‡] or dehydrogenated over platinum or nickel.[§] Disproportionation to *thymol* and *m-cresol* occurs when *piperitone* is treated with active carbon at 200°.^{||}

Using an alkaline solution of potassium permanganate Schimmel and Co.[¶] obtained *α-hydroxy-α-methyl-α'-isopropyl-adipic acid* (IX), *γ-acetyl-α-isopropylbutyric acid* (X) and *α-isopropylglutaric acid* (XI), thus proving conclusively the position of the ethylenic linkage. The ketone employed in these experiments was derived from Japanese peppermint oil.

By carrying out the oxidation in neutral solution Roberts** obtained *diosphenol* (XII), a product which was obtained also by Penfold.^{††} Simonsen^{‡‡} prepared from *d-piperitone* 1-*γ-acetyl-α-isopropylbutyric acid* (X) and from this *α-isopropylglutaric acid* (XI), which was, however, optically inactive. With hydrogen peroxide, *piperitone* gives the *oxide* (XIII),^{§§} which is also formed by the autoxidation of the ketone.^{|||} Hydrogenation of the *dl-oxide* gives *dl-1-hydroxymenthone* (XIV), m.p. 89–90°.^{¶¶}

Piperitone yields a number of derivatives well suited for its characterisation. The observation that it yields on treatment

* *J. Proc. Roy. Soc. New South Wales*, 1923, **57**, 215.

† *J.C.S.* 1923, **123**, 2925.

‡ Borgwardt and Schwenk, *J. Amer. C.S.* 1934, **56**, 1185.

§ Dewar and Read, *J.C.S.* 1936, p. 1781.

|| Kimura, *J. Soc. Chem. Ind. Japan*, 1930, **33**, 301 B.

¶ Schimmel's Report, 1910, Oct. p. 102.

** *J.C.S.* 1915, **107**, 1466.

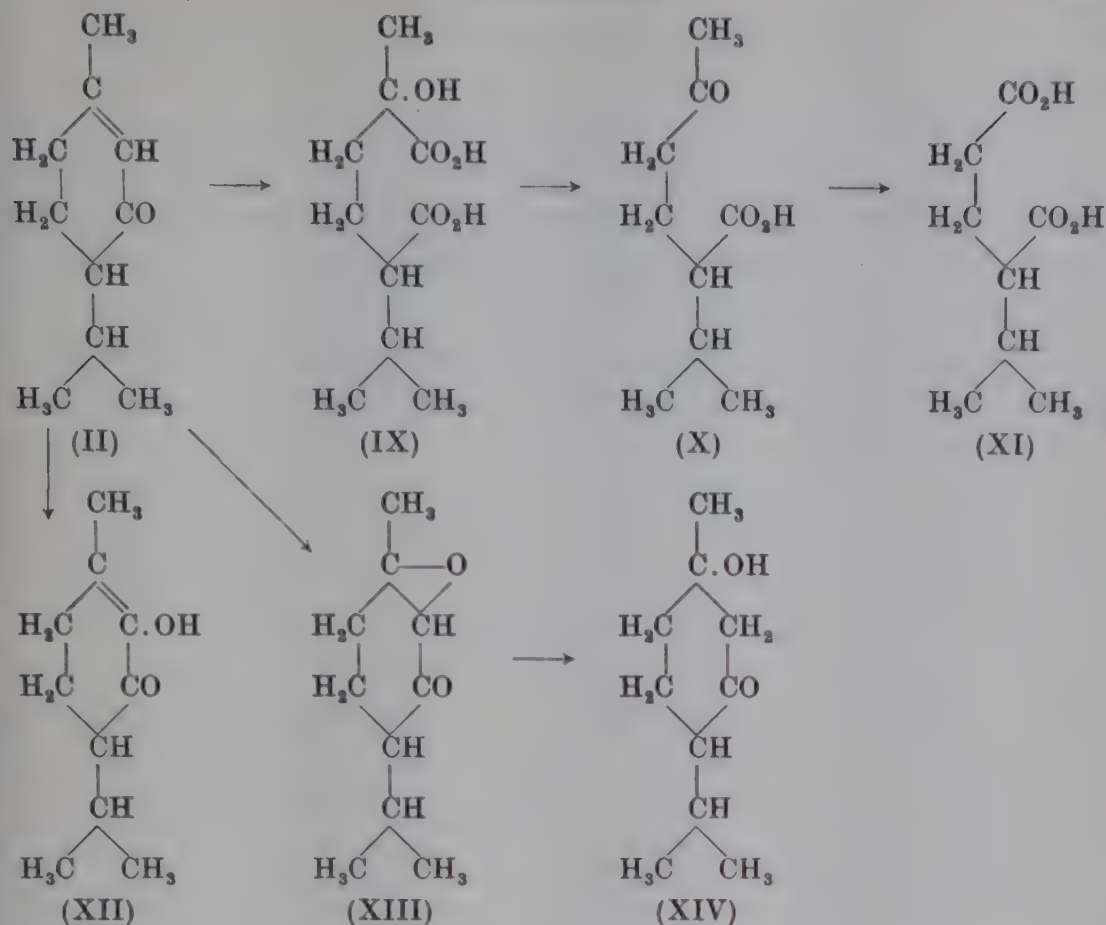
†† Compare Read, Smith and Bentivoglio, *J.C.S.* 1922, **121**, 584 footnote.

‡‡ *J.C.S.* 1921, **119**, 1646.

§§ Kötze and Hofmann, *J. pr. Chem.* 1925 [ii], **110**, 121; see also Rupe and Refardt, *Helv. Chim. Acta*, 1942, **25**, 836.

||| Treibs, *Ber.* 1933, **66**, 610.

¶¶ Read and Swann, *J.C.S.* 1937, p. 237.



with semicarbazide a mixture of two semicarbazones was originally made by Schimmel and Co.,* and has been confirmed by subsequent investigators. The conditions governing the formation and separation of these derivatives from the *dl*-ketone have been studied by Read and Smith,[†] who found the very sparingly soluble α -semicarbazone to melt at 226–227° and the β -semicarbazone at 174–176°. *dl*-Piperitone does not appear to yield a semicarbazido-semicarbazone, but, by treatment of the ketone with semicarbazide hydrochloride in alkaline solution, *semicarbazido-dl-piperitone*, m.p. 186–187°, was prepared, the *hydrochloride* of which melts at 165–167°. The semicarbazido derivative, when dissolved in dilute hydrochloric acid, yields a mixture of the α - and β -semicarbazones. From *d*-piperitone, Simonsen prepared the optically active α -semicarbazone, m.p. 193–194°, which in pyridine solution had $[\alpha]_D - 216.8^\circ$. The optically active form of the *l*-piperitone semicarbazone does not appear

* Schimmel's Report, 1910, Oct. p. 98.

† J.C.S. 1922, 121, 1866.

to have been described. *dl*-Piperitone phenylsemicarbazone has m.p. 191–192°.*

From *dl*-piperitone two oximes have been prepared,[†] the α -oxime, m.p. 118–119°, and the β -oxime, m.p. 88–89°, both of which yield the same *hydrochloride*, m.p. 157°. The α -oxime gives on treatment with bromine a *dibromoxime*; this substance, which is somewhat unstable, is stated by Simonsen to decompose at 142° and by Read, Smith and Bentivoglio at 133–140°. The action of acetic anhydride on the α -oxime brings about aromatisation and formation of thymylamine.[‡] The preparation of the oxime of *d*-piperitone was investigated by Simonsen, who found that when the method of Lapworth and Steele[§] was adopted, in addition to the *dl*-oxime, a liquid optically active oxime was obtained, though in the presence of an excess of alkali only the racemic oxime was formed. Read and Smith have also shown that *l*-piperitone oxime is an oil ($[\alpha]_D + 238.1^\circ$ in benzene). When an excess of hydroxylamine is used, *dl*-piperitone- α -hydroxylamino-oxime, m.p. 176°, and *dl*-piperitone- β -hydroxylamino-oxime, m.p. 185–186°, are obtained;^{||} Simonsen described the acetate of *d*-piperitone hydroxylamino-oxime, m.p. 156–157° ($[\alpha]_D - 20.42^\circ$ in methyl alcohol), but he was unable to crystallise the hydroxylamino-oxime itself.

As has been mentioned already, Read and Smith[¶] made the interesting observation that piperitone condenses readily with benzaldehyde in the presence of alkali to yield a crystalline benzylidene derivative. This substance has been shown to be polymorphic, the α -modification, m.p. 59–60°, crystallising in pale yellow prisms, the β -, m.p. 63–64°, in tabular form with a much more pronounced yellow colour, and the γ -form, m.p. 69–70°, in faint yellow needles.** The γ -form is the most stable and in its presence neither the α - nor the β -form can be obtained. The benzylidene derivative yields a somewhat unstable *hydrobromide*, m.p. 91–95°, and on reduction with sodium and alcohol

* Naves, *Helv. Chim. Acta*, 1943, **26**, 172.

† Simonsen, *loc. cit.* p. 1652; Read, Smith and Bentivoglio, *ibid.* 1922, **121**, 588.

‡ Cooke and Macbeth, *J.C.S.* 1937, 1593.

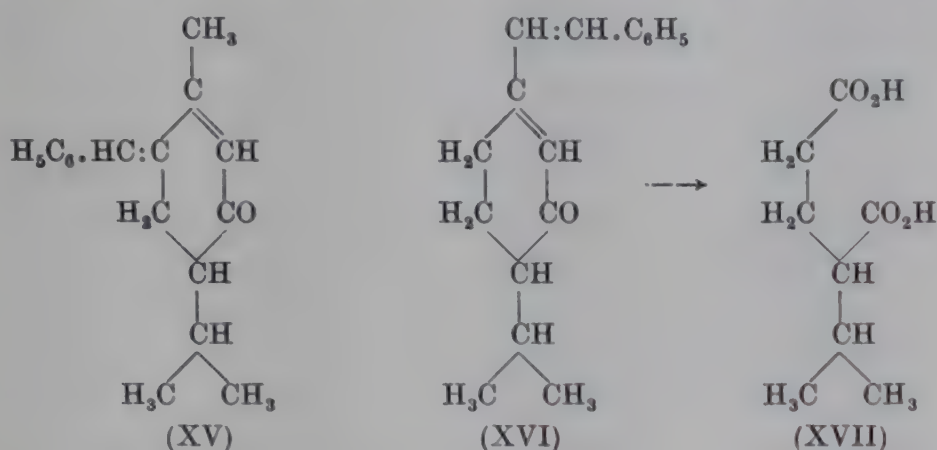
§ *Ibid.* 1911, **99**, 1884.

|| *Ibid.* 1922, **121**, 2292; see also Earl, Johnson and McKean, *J. Proc. Roy. Soc. New South Wales*, 1938, **72**, 109.

¶ *J.C.S.* 1921, **119**, 779; 1922, **121**, 575.

** Dewar, Morrison and Read, *ibid.* 1936, p. 1598.

is converted into *benzyl-p-menthenol*, b.p. 197–210°/18 mm. (*phenylurethane*, m.p. 140–141°). Other reactions of this substance have been described by Read, Smith and Hughesdon,* for details of which reference should be made to the original memoir. The condensation of *dl*-piperitone with other aldehydes has been studied by Earl and Read,† who have also established the constitution of these substituted piperitones. It had been suggested originally by Simonsen‡ that benzylidene-*dl*-piperitone was probably represented by (XV), owing to the activation of



the 6-position by the adjacent ethylenic linkage. No experimental evidence in support of this suggestion was advanced, and it has been shown by Earl and Read that since the benzylidene derivative gives on oxidation with potassium permanganate α -isopropylglutaric acid (XVII) it must be represented by formula (XVI). It is of interest that the activating influence of the grouping —CO—CH:CH— should be exerted outside the ring.

The *bis-nitroso*-derivative of *dl*-piperitone was first prepared by Roberts,§ and later by Read and Smith. It is somewhat unstable and melts at 97–98°.

When *dl*-piperitone is treated with potassium cyanide in alcoholic solution it yields a dicyclic *anhydramide* (XVIII), b.p. 151–153°/13 mm., which is insoluble in alkalis. It thus reacts with this reagent in a similar manner to pulegone (compare p. 380).||

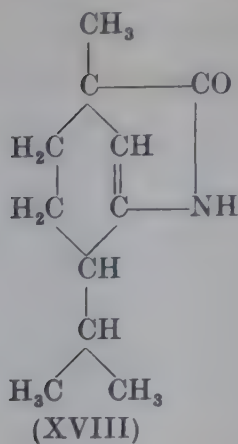
* *J.C.S.* 1924, 125, 134.

† *Ibid.* 1921, 119, 1646.

|| Read and Watters, *ibid.* 1929, p. 2168.

† *Ibid.* 1926, p. 2072.

§ *Ibid.* 1915, 107, 1466.

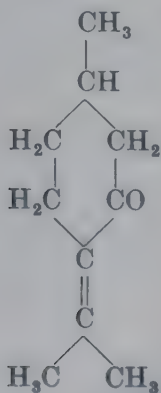


The action of the Grignard reagent with *dl*-piperitone has been studied by Read and Watters,* and has been shown to yield α -terpinene derivatives.

In view of its ready conversion into menthone, menthol and thymol, piperitone has become of considerable technical importance. Hughesdon, Smith and Read† have directed attention to the fact that *l*-piperitone always occurs in nature in association with *l*- α -phellandrene and *l*-piperitol, and it is possible that some relationship exists between these substances, although as has been pointed out by Simonsen, *d*-piperitone occurs in association with Δ^4 -carene. In this connection attention may also be directed to a communication by Penfold and Morrison‡ on the use of the piperitone content of eucalyptus oils as a means of distinguishing closely related varieties.

PULEGONE

($\Delta^{4(8)}$ -*p*-*Menthen-3-one* or
1-*Methyl-4-isopropylidenecyclohexan-3-one*)



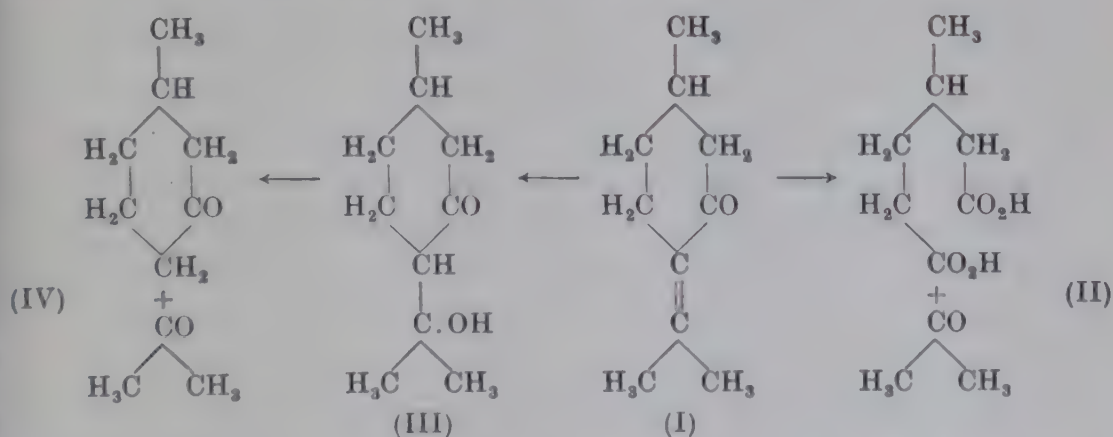
* *J.C.S.* 1929, p. 2168.

† *J. Proc. Roy. Soc. New South Wales*, 1927, 61, 54.

† *Ibid.* 1923, 123, 2925.

d-Pulegone, $C_{10}H_{16}O$, is found somewhat widely distributed in nature, but its occurrence is confined apparently to oils derived from the Labiatae.* It can readily be isolated in quantity from the pennyroyal oils derived from *Mentha Pulegium* and *Hedeoma pulegioides*. Although *l*-pulegone has not been described, in view of its wide distribution and the facility with which it can be obtained pure, *d*-pulegone has been studied exhaustively.

d-Pulegone was first isolated in a relatively pure condition by Kremers from the oil of *H. pulegioides*, but he erroneously ascribed to it the formula $C_{10}H_{18}O$, and it was not until the investigations of Beckmann and Pleissner† that its composition, $C_{10}H_{16}O$, was correctly determined and its ready conversion into menthone and menthol observed. In the following year Semmler‡ showed that the ketone, on oxidation with potassium permanganate, gave acetone and β -methyladipic acid (II) and he suggested therefore that it was probably $\Delta^{4(8)}$ -*p*-menthen-3-one (I). Confirmatory evidence in support of this constitution was furnished shortly afterwards by Wallach,§ who found that when the ketone was digested with formic acid, or heated to 250° under pressure, it underwent decomposition with the formation of acetone and 1-methylcyclohexan-3-one (IV), the hydroxy-ketone (III) being probably an intermediate stage in the reaction. The same decomposition results on prolonged digestion of the ketone with a water-alcohol solution of potassium hydroxide|| or by the action of sulphuric acid (75 per cent.).¶



* Compare Gildemeister and Hoffmann, *Die Ätherischen Öle*, 1928, Vol. I, 560.

† *Annalen*, 1891, 262, 1.

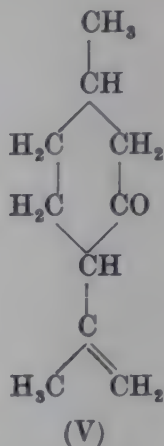
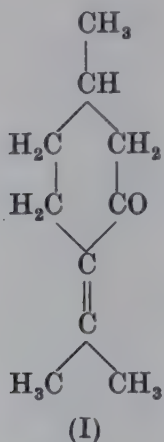
‡ *Ber.* 1892, 25, 3519.

§ *Annalen*, 1896, 289, 337.

|| Wallach, *ibid.* 1909, 365, 243.

¶ Léser, *Ann. chim.* 1912 [viii], 26, 235.

No doubt as to the homogeneity of the ketone from pennyroyal oil appears to have arisen until the investigations of Grignard and Savard.* According to these authors, when the pulegone fraction of the oil is oxidised with ozone it yields both acetone and formaldehyde. From the yield of the aldehyde and ketone Grignard and Savard concluded that pulegone from pennyroyal oil is a mixture of pulegone (I) (82–85 per cent.) and isopulegone (V) (15–18 per cent.). The latter ketone does not react with



sodium hydrogen sulphite and they stated that, by taking advantage of this, they had succeeded in separating natural “pulegone” into pulegone and isopulegone.

These conclusions have been criticised adversely by Hugh, Kon and Linstead[†] and by Naves,[‡] who have been unable to isolate any isopulegone from pennyroyal oil from various sources. This question is discussed further on p. 386.

Pulegone has not been prepared synthetically[§] by any direct process, although it was observed by Tiemann and Schmidt^{||} that it could be obtained from citronellal. As was mentioned on p. 80, this aldehyde (VI) on treatment with acetic anhydride yields isopulegol acetate (VII), from which isopulegol (VIII), is obtained on hydrolysis. Oxidation of the latter leads to isopulegone (V), which can be readily isomerised to pulegone (I) (see p. 388).

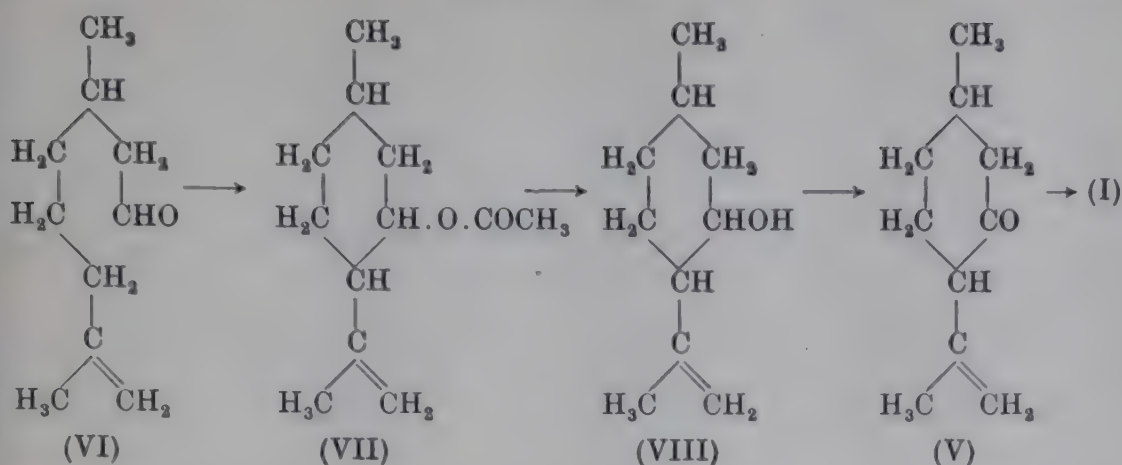
* *Compt. rend.* 1925, **181**, 589; 1926, **182**, 422; *Bull. Soc. chim. Belg.* 1927, **36**, 101.

† *J.C.S.* 1927, p. 2585.

‡ *Helv. Chim. Acta*, 1943, **26**, 162.

§ The “synthetic pulegone” prepared by Wallach (*Annalen*, 1898, **300**, 268) by the condensation of acetone and 1-methylcyclohexan-3-one has since been found to have a different constitution (Wallach, *Annalen*, 1912, **394**, 380).

|| *Ber.* 1896, **29**, 913; 1897, **30**, 22.



Pulegone is a pleasant smelling camphoraceous oil, which, as was observed by Baeyer and Henrich,* can be purified most readily by the crystalline compound which it forms with sodium hydrogen sulphite and from which it can be regenerated by the action of alkali. The ketone purified in this manner was found by Wallach† to have b.p. 221–222°, d 0.936, n_D 1.4846, whilst Grignard and Savard‡ found b.p. 84°/6 mm., d_4^{15} 0.9346, n_D 1.4894, $[\alpha]_D + 21^\circ$.§ In agreement with the assigned constitution the molecular refraction shows a considerable exaltation (+0.57).||

A large number of derivatives are available for the characterisation of pulegone, the most satisfactory, perhaps, being bis-nitrosopulegone, m.p. 81.5°, described originally by Baeyer and Henrich,⁹ or the 2:4-dinitrophenylhydrazone, m.p. 142°. **

The absorption spectrum of the ketone in the ultra-violet has been examined by several workers;^{††} the results confirm the conjugation of the ethylenic linkage with the carbonyl group.

With palladinised charcoal at 175°, pulegone gives a mixture of menthone and thymol.²² The reduction of pulegone has been studied by numerous investigators. Using sodium and alcohol as the reducing agent Beckmann and Pleissner²³ obtained

* *Ber.* 1895, 28, 652.

† *Ibid.* p. 1965.

* *Loc. cit.*

* Compare Kon, *J.C.S.* 1930, p. 1618.

¹¹ Auwers and Eisenlohr, *J. pr. Chem.* 1910 [ii], **82**, 137; 1911 [ii], **84**, 36; Simpson, *J.C.S.* 1939, p. 886.

† *Ber.* 1895, 28, 653.

** Brady, *J.C.S.* 1931, p. 756.

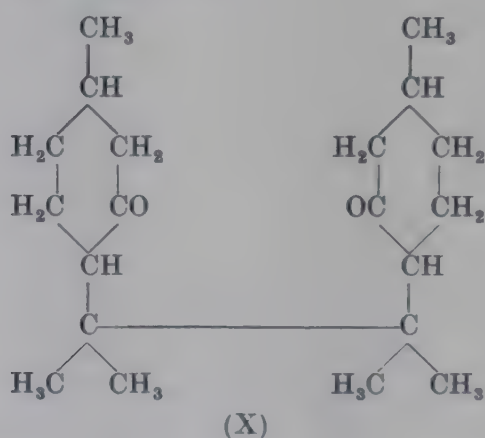
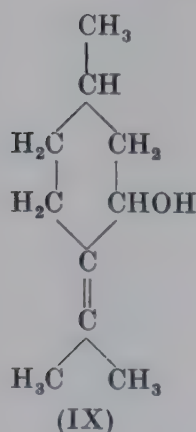
†† Crymble, Stewart, Wright and Rae, *J.C.S.* 1911, **99**, 1265; Purvis, *ibid.* 1924, **125**, 414; Savard, *Bull. Soc. chim.* 1928 [iv], **43**, 524; Lowry and Lishmund, *J.C.S.* 1935, p. 1313; Naves and Papazian, *Helv. Chim. Acta*, 1942, **25**, 1023, 1046.

* Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

" *Annalen*, 1891, 262, 30.

l-menthol, m.p. 38° ; simultaneously some menthone is produced. The action of the same reducing reagents, but at the ordinary temperature, was investigated by Tiemann and Schmidt.* They obtained a mixture of alcohols, which they concluded contained *pulegol* (IX), but they were unable to separate it from the menthol which was also present. Subsequently the reduction products from this reaction were examined by Paolini,[†] who, by fractional crystallisation of the hydrogen phthalates, was successful in separating *pulegol hydrogen phthalate* in the form of its strychnine salt. The *l*-pulegol, $[\alpha]_D -54.0^{\circ}$, regenerated from this, melted at 46° and boiled at $209-210^{\circ}$. Its reactions do not appear to have been studied.

Reduction with sodium and alcohol under pressure[‡] also yields *l*-menthol, but the optical rotatory power of the alcohol, $[\alpha]_D -12^{\circ}$, is much lower than that recorded by Beckmann and Pleissner. With aluminium amalgam in ethereal solution, Harries and Roeder[§] obtained *pulego-pinacone* (X), m.p. $118-119^{\circ}$, and this substance is formed also, together with menthone, when the reduction is carried out electrolytically in alkaline solution.^{||} With sodium amalgam Harries and Roeder obtained a mixture of the pinacone, menthone and menthol.



Attempts to reduce pulegone to pulegol, by the use of aluminium isopropoxide, have usually resulted in the formation of a mixture of $\Delta^{2:4(8)}$ - and $\Delta^{3:8(9)}$ -*p*-menthadienes,[¶] though Short

* Ber. 1896, **29**, 914.

[†] Atti R. Accad. Lincei, 1919 [v], **28**, II, 190, 236.

[‡] Skworzow, J. pr. Chem. 1911 [ii], **84**, 424.

[§] Ber. 1899, **32**, 3367.

^{||} Law, J.C.S. 1912, **101**, 1029.

[¶] Grubb and Read, J.C.S. 1934, p. 242; Dœuvre and Perret, Bull. Soc. chim. 1935 [v], **2**, 298.

and Read* have shown that pulegol and isopulegol are also present in small amount.

Catalytic hydrogenation leads to a variety of products depending upon the conditions used. Haller and Martine† were the first to investigate reduction by the Sabatier-Senderens process and, with a nickel catalyst at 150–200°, they obtained a *d*-menthone, $[\alpha]_D + 5^\circ$ to $+ 8^\circ$, which gave a liquid oxime and a benzylidene derivative, m.p. 140°. At a somewhat lower temperature (150–160°) a mixture of menthols was obtained, from which, by crystallisation of either the menthol or its hydrogen phthalate, (i) *l*-menthol, m.p. 43–44°, $[\alpha]_D - 46.4^\circ$, (ii) *iso*-menthol, m.p. 84–85°, $[\alpha]_D - 30^\circ$, and (iii) a liquid *d*-menthol, $[\alpha]_D + 2.6^\circ$, were separated. Somewhat different results were recorded by Skita and Ritter,‡ who isolated *p*-cymene, *p*-menthane, menthone and a little menthol. This divergence is probably accounted for by a slight difference in experimental conditions, since, according to Sabatier and Gaudion,§ when the reaction is carried out at 350–360°, a mixture of *m*-cresol and thymol is obtained.||

Ipatiev and Balatschinsky¶ have examined the products formed when the reduction is carried out under high pressures with a nickel catalyst; at 280° *p*-menthane is obtained, whilst at 220–240° *d*-menthone ($[\alpha]_D + 21.4^\circ$) is the main product of the reaction. With a kieselguhr catalyst *p*-cymene and thymol are formed.**

Hydrogenation at the ordinary temperature in the presence of either colloidal palladium or platinum black proceeds smoothly. Skita and his collaborators†† using the former catalyst obtained a *d*-menthone ($[\alpha]_D + 11^\circ$), whilst Vavon‡‡ with platinum black obtained a *d*-menthone with a somewhat lower optical rotatory power ($[\alpha]_D + 6.4^\circ$).§§

* J.C.S. 1939, p. 1306.

† Compt. rend. 1905, 140, 1298.

‡ Ber. 1911, 44, 669.

§ Compt. rend. 1919, 168, 671.

|| Compare Gonzalez, Anal. Fis. Quim. 1930, 28, 247.

¶ Ber. 1911, 44, 3463.

** Ipatiev and Petrov, *ibid.* 1927, 60, 2546.

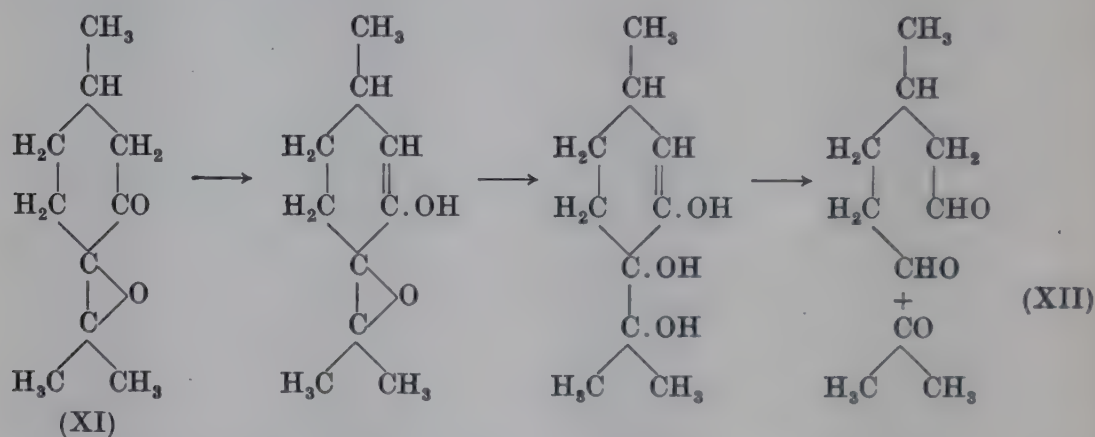
†† *Ibid.* 1910, 43, 3394; 1915, 48, 1496; 1922, 55, 140.

‡‡ Compt. rend. 1912, 155, 287.

§§ The menthones and menthols which have been prepared by the hydrogenation of *d*-pulegone are mixtures consisting essentially of *isomenthones* and *isomenthols* (compare p. 240).

The oxidation of pulegone with ozone has been studied by Harries and his students.* Contrary to expectation, the oxidation does not yield a mixture of acetone and 1-methylcyclohexane-3:4-dione. The cyclic ketone is converted directly into β -methyladipic acid (II), a type of reaction not without analogy. The oxidation products with ozone and potassium permanganate are therefore in this case the same.

Prileschaev[†] has found that the ketone reacts readily with perbenzoic acid to give the *oxide* (XI), m.p. 43–44°, b.p. 137–138°/24 mm. On keeping, the oxide gradually liquefies and passes into an isomeride, b.p. 123–124°/25 mm., from which the *semicarbazone*, m.p. 210–211.5°, was prepared. The nature of the isomerism has not been determined. When the oxide is digested with dilute sulphuric acid it yields the *dialdehyde* (XII) and acetone; the mechanism of the reaction is indicated in the scheme given below.



With selenium dioxide, pulegone gives a *diketone* (XIII) and a *triketone* (XIV), the structures of which are confirmed by oxidation to α -methylglutaric acid (XV) and β -methyl- α -keto-glutaric acid (XVI) respectively.*

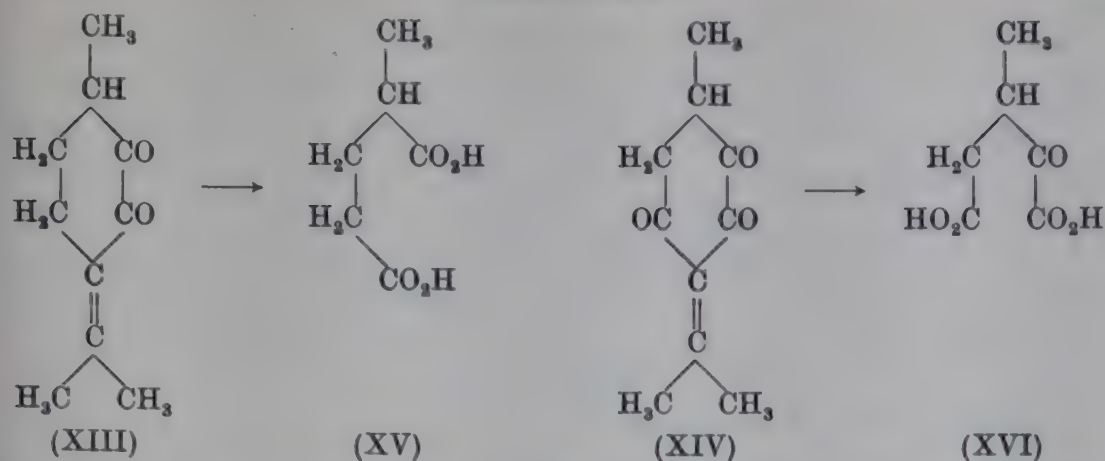
Pulegone is readily brominated to give a liquid *dibromide* (XVII), the reactions of which have been studied by Wallach and his collaborators.[‡] By the action of alkali the dibromide is converted into a liquid acid, *pulegenic acid*, which is not homo-

* *Annalen*, 1910, **374**, 300.

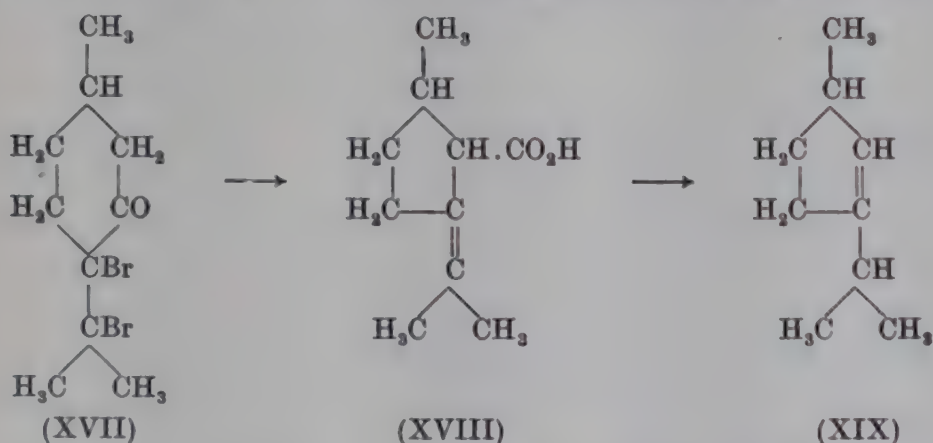
† *Bull. Soc. chim.* 1927 [iv], **41**, 687; see also Treibs, *Ber.* 1933, **66**, 1492.

‡ Cauquil, *Compt. rend.* 1939, **208**, 1156.

§ *Inter al.*, *Annalen*, 1896, **289**, 349; 1898, **300**, 259; 1903, **327**, 150; 1917, **414**, 234.



geneous, but consists largely of the acid represented by (XVIII). On distillation at the ordinary pressure pulegenic acid loses carbon dioxide with formation of the hydrocarbon, *pulegene* (XIX), the exocyclic ethylenic linkage having passed into the ring. For a description of the many interesting reactions of these *cyclopentene* derivatives reference should be made to the original memoirs, a discussion being outside the scope of this book.



By the distillation of the crude dibromide under the ordinary pressure it is decomposed, yielding, amongst other substances, *m*-cresol and 1-methylcyclohexan-3-one.*

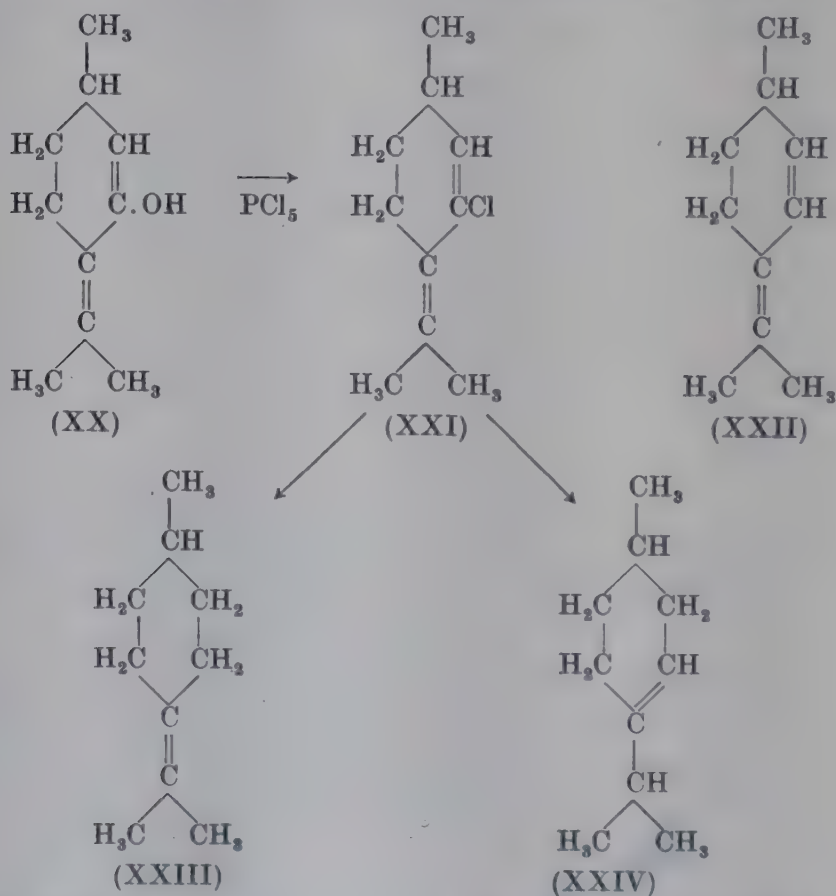
Pulegone hydrochloride (8-chloro-*p*-menthan-3-one) was prepared by Baeyer and Henrich† by the action of hydrogen chloride on the ketone in acetic acid solution. It crystallises in rhombic crystals, m.p. 24–25°, and is readily reconverted into the parent ketone by alkali. It is apparently more stable than the corresponding *hydrobromide*, m.p. 40.5°, which Beckmann and Pleissner‡ obtained by the action of hydrogen bromide in

* Klages, *Ber.* 1899, **32**, 2564. † *Ibid.* 1895, **28**, 653. ‡ *Annalen*, 1891, **262**, 1.

ligroin solution. This substance yields menthone on reduction with zinc dust and alcohol, whilst silver acetate in acetic acid regenerates the parent ketone. According to Harries and Roeder,* it is converted by the action of lead nitrate into a mixture of pulegone, isopulegone and 1-methylcyclohexan-3-one.

Cauquil and Mion† have shown that pulegone reacts with hypochlorous acid to give 5-chloro-8-hydroxymenthone, b.p. 134–135°/20 mm., d_4^{20} 1.0892, n_D^{23} 1.4951, $[\alpha]_{5780} + 13.3^\circ$, which gives a green colour with ferric chloride.

The interaction of pulegone and phosphorus pentachloride, investigated originally by Klages‡ and by Barbier,§ was later studied by Auwers.|| The main product of the reaction is a chloride (XXI) arising evidently from the enolic form of the ketone (XX). Reduction of the chloride with sodium and alcohol does not give the *p*-menthadiene (XXII), but a mixture of $\Delta^{4(8)}$ -*p*-menthene (XXIII) and Δ^3 -*p*-menthene (XXIV).



* Ber. 1899, 32, 3368.

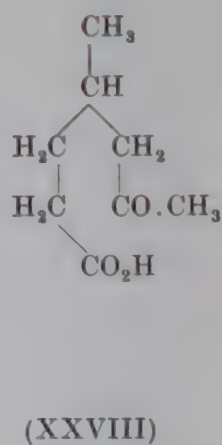
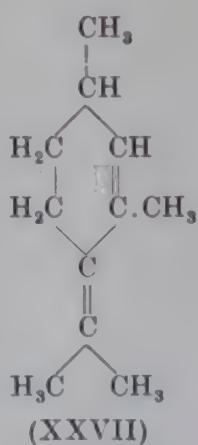
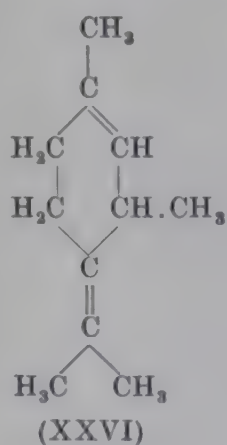
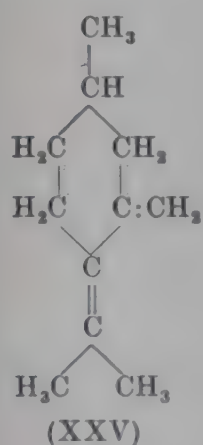
† Ber. 1899, 32, 2564.

|| Ber. 1909, 42, 4895.

‡ Bull. Soc. chim. 1940 [vi], 7, 659.

§ Compt. rend. 1892, 114, 126.

By the action of methyl magnesium iodide on pulegone, Grignard* prepared a hydrocarbon to which he gave the constitution (XXV), although he did not at the time offer any decisive experimental evidence in support thereof. This hydrocarbon has subsequently been investigated by Rupe and Emerich† and by Auwers and Eisenlohr.‡ The former suggested, since the hydrocarbon does not show any exaltation of its molecular refraction, that it is more probably represented by (XXVI), a view not shared by Auwers and Eisenlohr, who preferred the alternative formula (XXVII). Rupe, Schobel and Abegg§ attempted to obtain decisive evidence by an examination of the products formed on ozonolysis. By this degradation, acetone and γ -methyl- δ -acetylvaleric acid (XXVIII) were obtained. These substances can result from either of the hydrocarbons represented by (XXV) or (XXVII), the oxidation proceeding in a similar manner to that of pulegone itself. It is not improbable that methylpulegene is a mixture of the two hydrocarbons represented by the formulae (XXV) and (XXVII) and that it is not homogeneous.



When pulegone is allowed to react with methyl magnesium iodide, it is always found that a considerable quantity of the ketone is recovered apparently unchanged. A careful study of the action of various alkyl magnesium compounds on the ketone by Grignard and Savard|| has shown, however, that the oil

* *Thèse de Doctorat*, 1901, p. 94.

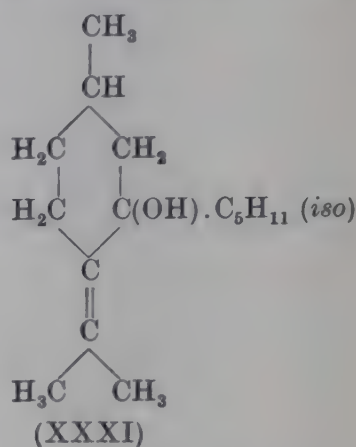
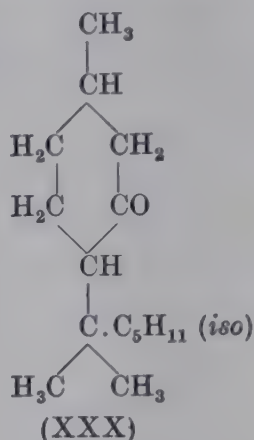
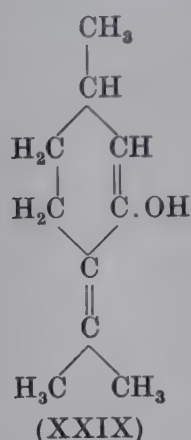
‡ *Ibid.* 1910, 43, 830.

† *Ber.* 1908, 41, 1750.

§ *Ibid.* 1912, 45, 1529.

|| *Compt. rend.* 1924, 179, 1573; 1926, 182, 422; *Bull. Soc. chim. Belg.* 1927, 36, 101; Grignard and Blanchon, *Bull. Soc. chim.* 1931 [iv], 49, 23.

recovered is not pulegone, but the enolic form of the ketone, *pulegenol* (XXIX). With *isoamyl* magnesium bromide, the ethylenic linkage in pulegone is attacked* to give *isoamyl-menthone* (XXX); an accompanying alcohol, formed in smaller yield, but not isolated in a pure condition, is probably the normal product (XXXI). Pulegenol is stated to be comparatively



stable. It can be distilled without change and has the following constants: b.p. $85^\circ/6$ mm., $d_4^{13^\circ}$ 0.916, $n_D^{13^\circ}$ 1.4831, $[\alpha]_D + 24.6^\circ$. It has been characterised by the preparation of a crystalline *benzoyl* derivative, m.p. 230° ; the *acetyl* derivative is an oil, from which the enol can be regenerated by water, thus affording a convenient method for its isolation and purification. By distillation in steam or by the action of alkalis, it is isomerised to the ketone. The ultra-violet absorption spectrum of pulegenol has been investigated by Savard.[†]

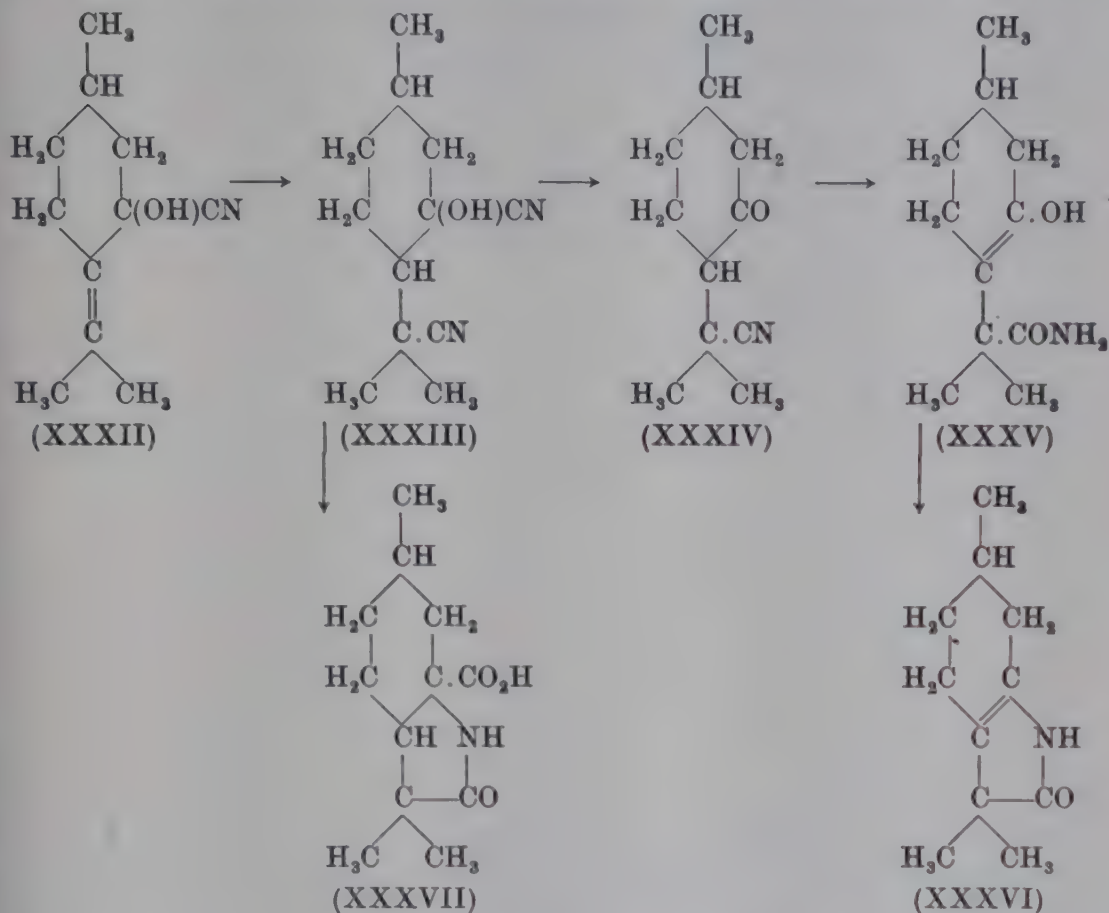
By the action of sodium cyanide solution containing hydrogen cyanide, Lapworth and Clarke[‡] prepared from pulegone *cyanomenthone cyanohydrin* (XXXIII), m.p. $195\text{--}197^\circ$, the normal cyanohydrin (XXXII) evidently having a transient existence. When an alcoholic solution of potassium cyanide and pulegone is warmed *menthonecarboxylic anhydramide* (XXXVI) is formed. The mechanism involved is probably the following: the primary product of the reaction, cyanomenthone cyanohydrin (XXXIII), loses hydrogen cyanide with formation of *cyanomenthone* (XXXIV), the *amide* of the enolic form of which (XXXV) then loses water with formation of the anhydramide (XXXVI).

* Dœuvre, *Bull. Soc. chim.* 1939 [v], 6, 1067.

† *Compt. rend.* 1928, 186, 1738.

‡ *J.C.S.* 1906, 89, 1869.

A further product of the reaction of potassium cyanide on pulegone is the *lactam* of *aminomenthane dicarboxylic acid* (XXXVII), a hydration product of the cyanohydrin (XXXIII).



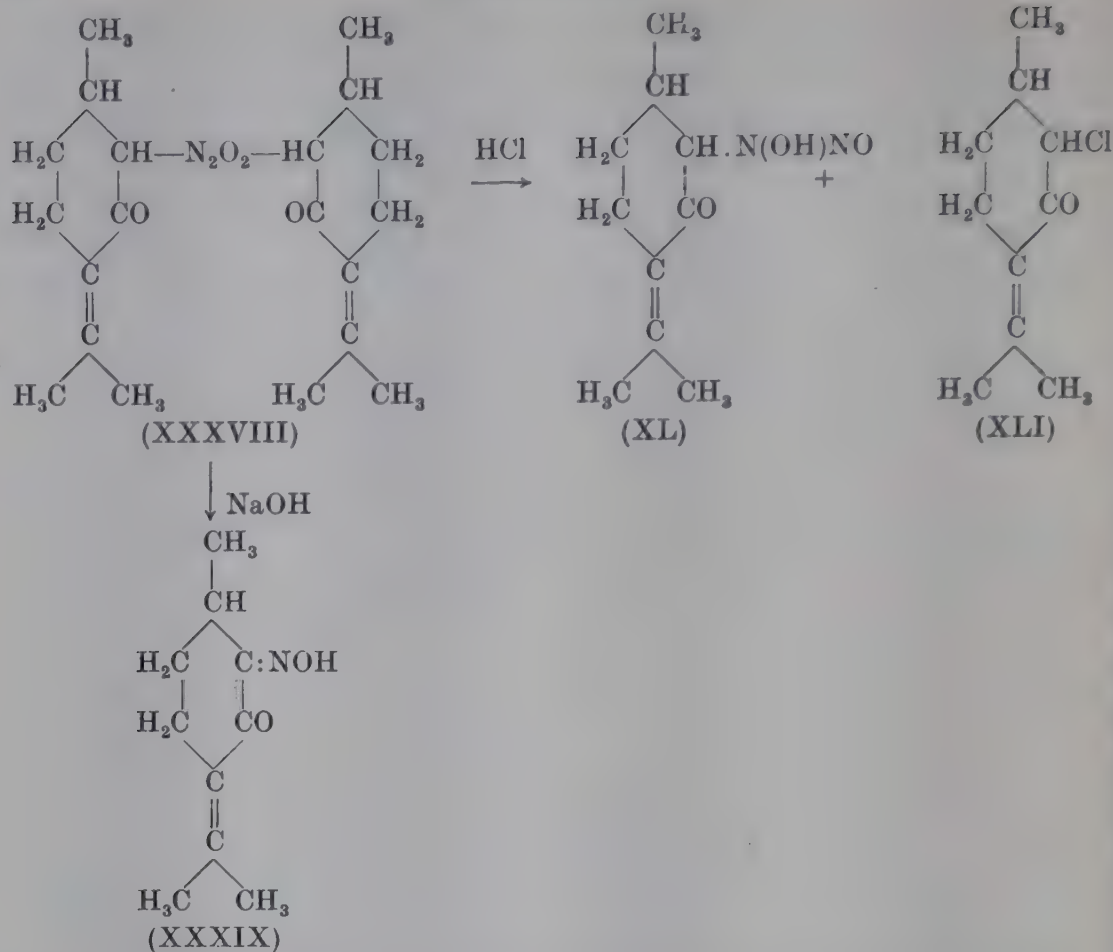
Bis-nitrosopulegone (XXXVIII), m.p. 81.5°, was obtained by Baeyer and Henrich* by the action of hydrochloric acid on a mixture of the ketone and amyl nitrite. The reactions of this well-defined body were subsequently studied by Baeyer and Prentice,† who found that on treatment with alkali it was converted into *isonitrosopulegone* (XXXIX), m.p. 122–127°, whilst by the action of hydrochloric acid, a mixture of the *nitrosylic acid* (XL), m.p. 115–116°, and the *chloro-ketone* (XLI), m.p. 124–125°, was formed.

With hydroxylamine pulegone yields a number of interesting derivatives. By the action of hydroxylamine hydrochloride on the ketone in the presence of sodium bicarbonate, Beckmann and Pleissner‡ obtained *pulegone hydroxylamine* (XLII), m.p.

* *Ber.* 1895, 28, 653.

† *Ibid.* 1896, 29, 1078.

‡ *Annalen*, 1891, 262, 6.



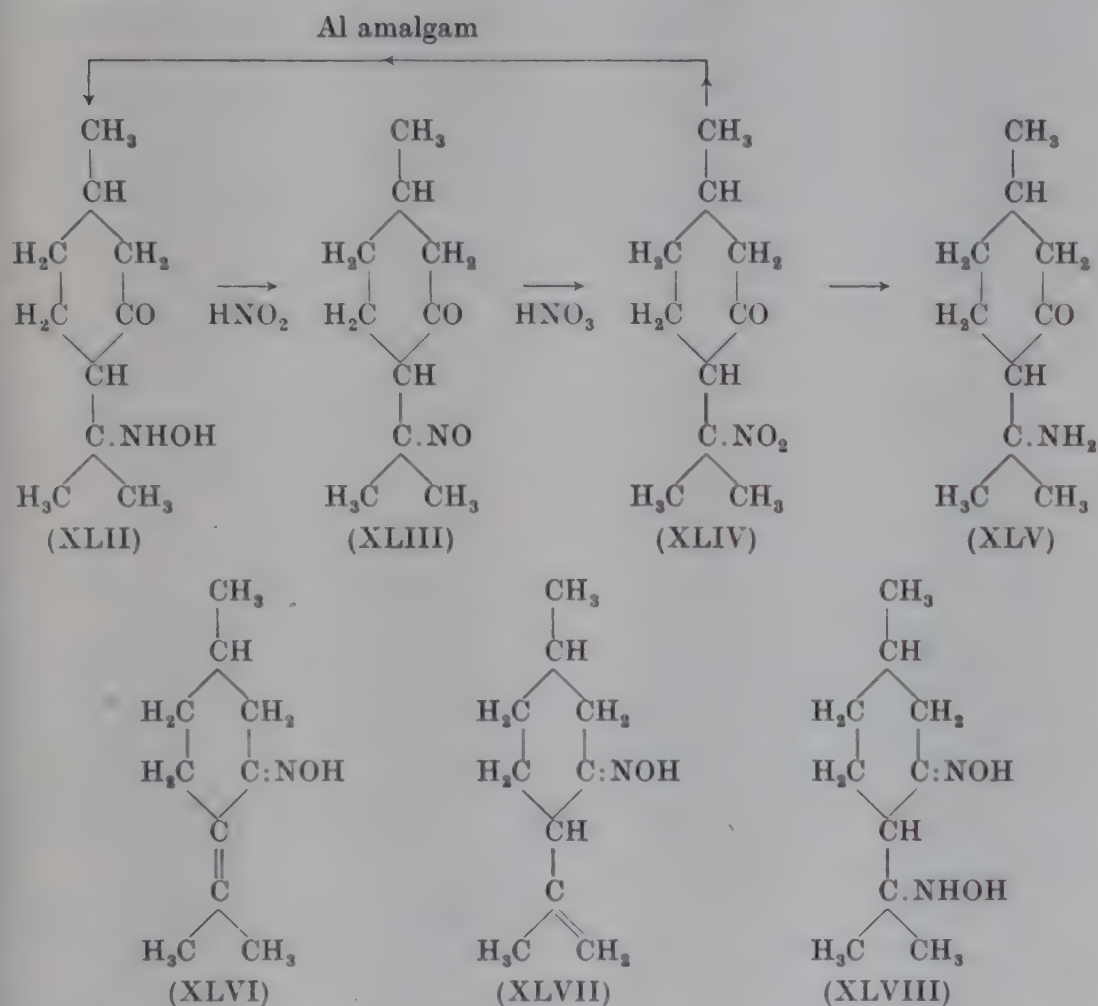
157°, by the addition of hydroxylamine to the ethylenic linkage. The constitution of this substance was determined by Harries and his collaborators.* They showed that on treatment with nitrous acid it gave 8-nitrosomenthone (XLIII), m.p. 35°, from which 8-nitromenthone (XLIV), m.p. 80°, could be prepared. Reduction of the latter with aluminium amalgam reconverted it into the hydroxylamine (XLII). It may be mentioned that Beckmann and Pleissner found that reduction of this substance with hydriodic acid gave a base, which must be 8-aminomenthone (XLV).

Treatment of pulegone under somewhat different conditions with hydroxylamine was shown by Wallach† to lead to a normal oxime, m.p. 120–121°. This is not, however, d-pulegoneoxime (XLVI) but d-isopulegoneoxime (XLVII). On hydrolysis with alkali pulegone is obtained, but by careful hydrolysis with oxalic acid it yields isopulegone, whilst if sulphuric acid is used as the

* Ber. 1898, 31, 1809; 1899, 32, 3357; 1903, 36, 659.

† Annalen, 1893, 277, 160; 1896, 289, 347; 1909, 365, 240.

hydrolytic agent a mixture of the two ketones is formed. Francesconi and Sanna* prepared a second *oxime*, m.p. 141°, by the action of hydrogen chloride on the oxime, m.p. 120–121°, in ethereal solution. This they considered to be the true *pulegone-oxime* (XLVI) but conclusive evidence of its constitution is not available.



Semmler[†] first prepared *pulegone hydroxylamino-oxime* (XLVIII), m.p. 118°, by the action of an excess of hydroxylamine on the ketone. It has been found by Cusmano[‡] that a second hydroxylamino-oxime, m.p. 145°, exists.

With hydrazine, pulegone gives *pulegone pyrazoline* (XLIX), b.p. 114°/11 mm., which according to Kishner and Sawadowski[§] yields carane (L) when distilled with potassium hydroxide; when heated with sodium ethoxide under pressure, however, Semmler

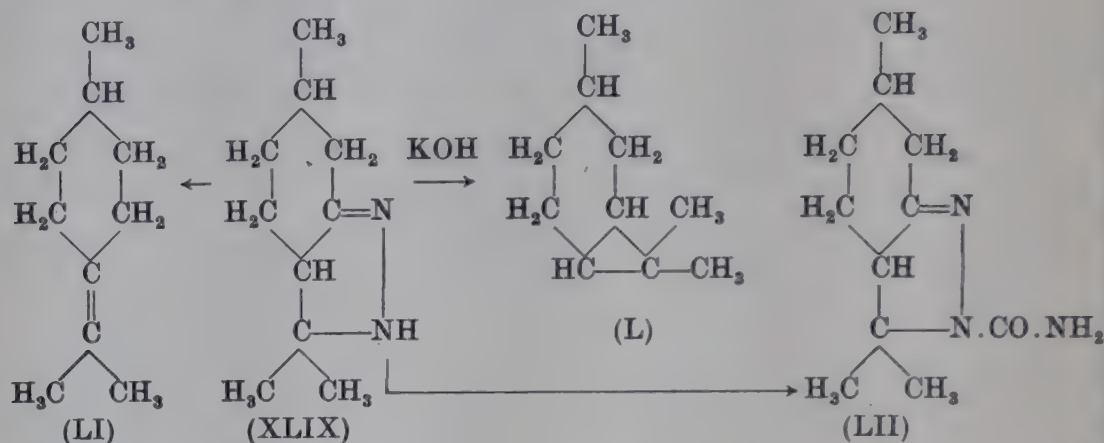
* *Gazzetta*, 1915, 45, 35.

‡ *Gazzetta*, 1909, 39, II, 453.

† *Ber.* 1905, 38, 146.

§ *J. Russ. Phys. Chem. Soc.* 1911, 43, 1132.

and Feldstein* showed that *dihydroterpinolene* (LI) is formed. With potassium cyanate it gives *carbaminyl pulegone pyrazoline* (LII), m.p. 156–157°, which may also be prepared by treating pulegone with semicarbazide at 100°.† The true *d-pulegone semicarbazone*, which is formed under less vigorous conditions, crystallises in prisms, m.p. 172°.‡ *d-Pulegone phenylsemicarbazone* has m.p. 142–143°.§



Although pulegone in most of its reactions shows marked stability, it also shows some tendency to decompose, yielding acetone and 1-methylcyclohexan-3-one. The condensation with ethyl acetoacetate, originally investigated by Barbier,^{||} has been found by Jupp, Kon and Lockton[¶] to give *pulegone acetone*, which has the constitution represented by (LIII) and not (LIV), as Barbier considered probable, although some evidence of the existence of the isomeride was obtained.

Reddelien** has shown that pulegone reacts normally with aniline in the presence of zinc chloride to yield the *anil* (LV), but at the same time addition of aniline to the ethylenic linkage also occurs with formation of the substances represented by (LVI) and (LVII). The ketone, however, reacts abnormally with both isatin and salicylaldehyde, fission into acetone and 1-methylcyclohexan-3-one occurring in each case.††

* Ber. 1914, **47**, 385. These authors considered their material to be the hydrazone, but it was probably the pyrazoline. It is doubtful whether the true hydrazone has been prepared.

† Busse and Gurewitsch, Ber. 1930, **63**, 2209.

‡ Baeyer and Henrich, *ibid.* 1895, **28**, 653.

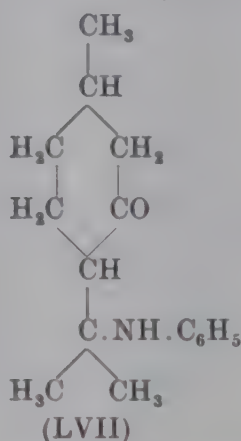
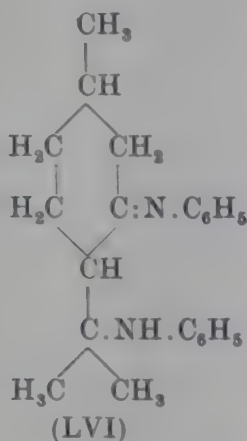
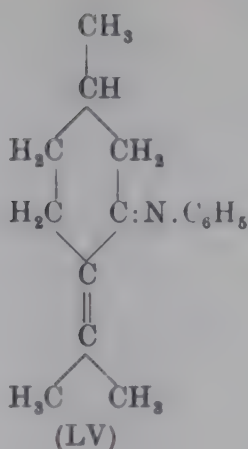
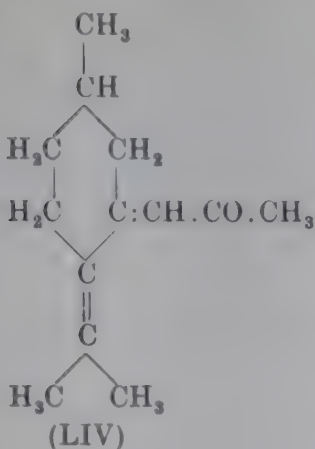
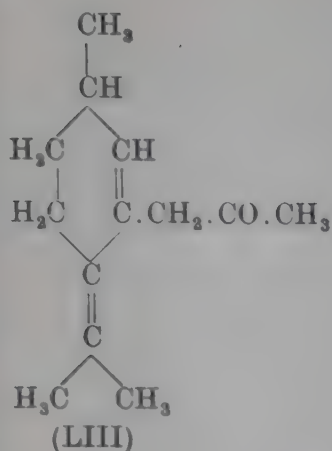
§ Naves, *Helv. Chim. Acta*, 1943, **26**, 172.

|| *Compt. rend.* 1898, **127**, 870.

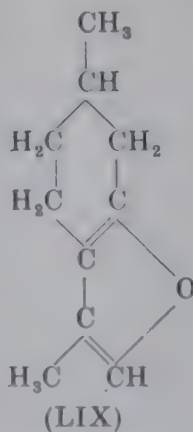
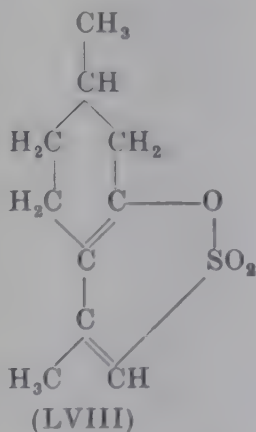
¶ *J.C.S.* 1928, p. 1639.

** Ber. 1920, **53**, 346.

†† Borsche, *Annalen*, 1910, **377**, 102; Borsche and Geyer, *ibid.* 1912, **393**, 31.



Treibs* has shown that pulegone reacts with sulphuric acid in acetic anhydride to give *pulegenol sulphonic cyclo-ester* (LVIII), m.p. 85°, a reaction which is recommended for characterisation of the ketone. On heating, sulphur dioxide is evolved, and the *oxide* (LIX) is formed; this is probably identical with *menthofuran*, isolated from peppermint oil by Carles† and investigated by Wienhaus.‡



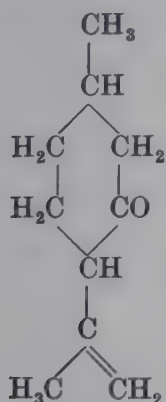
* Ber. 1937, 70, 85.

‡ Z. angew. Chem. 1934, 47, 415.

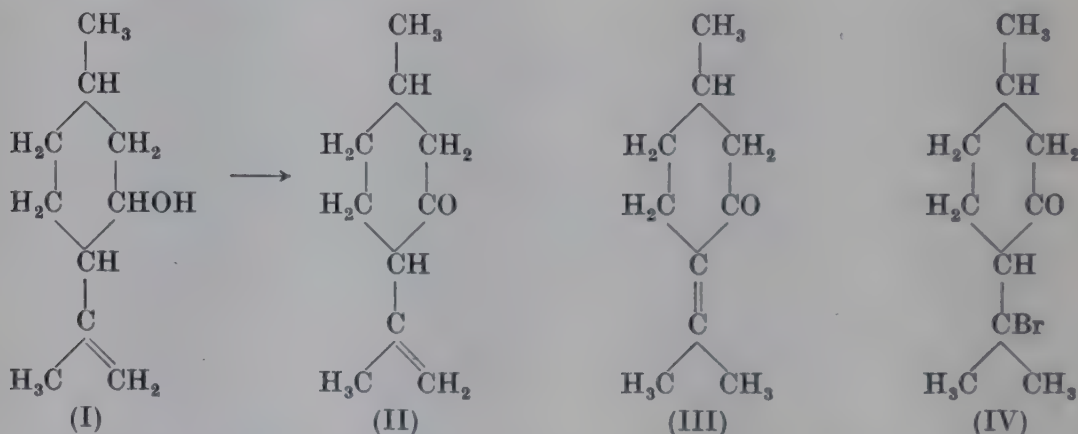
† Schimmel's Report, 1930, p. 65.

ISOPULEGONE

($\Delta^{8(9)}$ -*p*-Menthen-3-one or
1-Methyl-4-isopropenylcyclohexan-3-one)



During their investigation of the alcohol *isopulegol* (I), formed by the cyclisation of citronellal (p. 80), Tiemann and Schmidt* showed that on oxidation it was converted into a ketone, *isopulegone* (II). It is only recently that its occurrence in nature has been reported.



In 1925 Grignard and Savard[†] found that when pulegone, separated from pennyroyal oil by fractional distillation, was oxidised with ozone, not only acetone but also formaldehyde was produced in a yield corresponding to an admixture of 15–18 per cent. of *isopulegone* with the pulegone (III). In later communications these authors[‡] extended their experiments, and, after removal of the pulegone by means of sodium hydrogen sulphite, they prepared what they regarded as pure *isopulegone*

* *Ber.* 1896, 29, 914.

† *Compt. rend.* 1925, 181, 589.

‡ *Ibid.* 1926, 182, 422; *Bull. Soc. chim. Belg.* 1927, 36, 101.

from pennyroyal oil. The yield of *isopulegone* was found to be about 15 per cent. of the "pulegone" fraction of the oil, in good agreement with the results obtained on ozonolysis. The occurrence of *isopulegone* in pennyroyal oil has been questioned by Hugh, Kon and Linstead.* They examined a number of samples of this oil, but they were quite unable to detect any of this ketone. They further pointed out that the constants of Grignard and Savard's ketone differed very widely from those observed by Harries and Roeder† for *isopulegone*, and also from those specimens of the ketone which they prepared by various methods. The values are given in the subjoined table.

			Grignard and Savard	Harries and Roeder	Hugh, Kon and Linstead
B.p.	78°/5 mm.	98–100°/13 mm.	101–102°/17 mm.
d	$d_4^{14.4^\circ}$ 0.9097	$d^{19.5^\circ}$ 0.9192	$d_4^{20^\circ}$ 0.9208
n_D	$n_D^{14^\circ}$ 1.4633	—	$n_D^{20^\circ}$ 1.4666
$[\alpha]_D$	+ 34°	Laevorotatory	+ 24.7°
M.p. semicarbazone			172°	172–174°	176–177°

Hugh, Kon and Linstead suggested that Grignard and Savard's *isopulegone* was in reality *menthone*, the presence of which in pennyroyal oil had already been reported by Tétay.‡ This suggestion seems improbable since Grignard and Savard were acquainted with Tétay's investigation, to which they referred. Further, the French investigators found that their *isopulegone* could be converted into *pulegone hydrobromide* (IV) by the action of hydrogen bromide, and reduced to *isopulegol*, and their view was supported by the experiments of Rupe and Héretier§ on the rotatory dispersion of the ketone. It must, however, be admitted that the constants of the natural ketone show a very marked difference from those of all other specimens, and, on the present evidence, it must be regarded as doubtful if pennyroyal oil contains any *isopulegone*, more especially so in view of the marked instability of the ketone (see below). Further experiments on this subject would be very desirable.

isoPulegone is a colourless oil with an odour indistinguishable from that of *pulegone*. The ketone, when prepared either from *isopulegol* or from *pulegone hydrobromide*, is usually stated to

* J.C.S. 1927, p. 2585; Kon, *ibid.* 1930, p. 1617; see also Naves, *Helv. Chim. Acta*, 1943, 26, 162.

† Ber. 1899, 32, 3368.

‡ Bull. Soc. chim. 1902 [iv], 27, 186.

§ Annalen, 1927, 459, 171.

be laevorotatory,* but, according to Hugh, Kon and Linstead, this is not the case. The laevorotation observed by previous investigators has apparently in all cases been due to the presence of impurities, and the pure ketone is strongly dextrorotatory ($[\alpha]_D + 24^\circ$ approximately). The laevorotatory form of the ketone has not been prepared, nor has the *dl*-ketone, although derivatives of the latter are known.†

The ketone can be characterised most readily by the preparation of the *semicarbazone*, which crystallises in needles, m.p. $175-176^\circ$. The *dl*-semicarbazone, which according to Harries and Roeder is much more sparingly soluble, melts at 183° . Dœuvre‡ has prepared what he considers to be an isomeric *semicarbazone*, m.p. 156° , but it is not improbable that this is actually a pyrazoline derivative (compare p. 383).

*iso*Pulegone is prepared most conveniently by the oxidation of *isopulegol*, and is always a mixture of the active and racemic forms. It can be purified by crystallisation of the *semicarbazone*, from which it can be regenerated by hydrolysis with oxalic acid. If this hydrolysis be carried out with small quantities of material (20 grammes), very little pulegone is formed simultaneously. As was shown by Harries and Roeder the latter can be removed by treatment with sodium amalgam, when the pulegone is converted into the pinacone (see p. 374), whereas the *isopulegone* remains unaffected.

*iso*Pulegone can also be obtained by a method first used by Harries and Roeder, the removal of hydrogen bromide from pulegone hydrobromide (IV) with basic lead nitrate. The yield of the ketone by this reaction is, however, very variable and at times consists solely of pulegone.

Tiemann and Schmidt§ found that, on reduction of the ketone with sodium and alcohol, *isopulegol* was formed, whilst, on digestion with formic acid, it was decomposed into acetone and 1-methylcyclohexan-3-one. The latter decomposition is obviously preceded by isomerisation to pulegone. This change proceeds with remarkable facility and has been studied quantitatively by Hugh, Kon and Linstead. In the presence of traces of sodium

* Since *isopulegone* has two asymmetric carbon atoms, two *d*- and two *l*-forms, together with the corresponding *dl*-forms, are theoretically capable of existence.

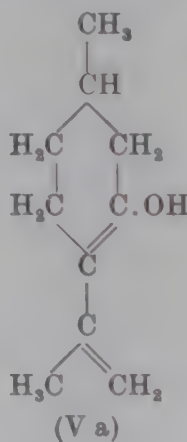
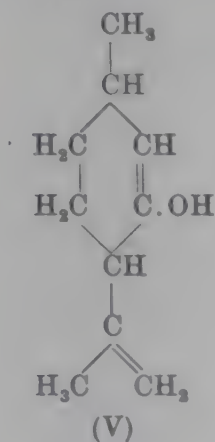
† Beilstein, *Handbuch der organischen Chemie*, VII, 85.

‡ *Bull. Soc. chim.* 1933 [v], 53, 589.

§ *Ber.* 1897, 30, 28.

ethoxide the conversion of *isopulegone* into *pulegone* is almost instantaneous, whilst with baryta it is complete in about two hours; piperidine appears to have no action. With hot mineral acids the same change takes place, but quantitative measurement of the speed of the reaction is not possible, since decomposition into acetone and 1-methylcyclohexan-3-one takes place simultaneously.

Grignard and Savard observed that *isopulegone*, like *pulegone*, yields, on treatment with alkyl magnesium halides, the enolic modification, *isopulegenol* (V) or (V a). The following constants were found for the enol: b.p. $80-81^{\circ}/6$ mm., $d_4^{14^{\circ}}$ 0.8965, $n_D^{14^{\circ}}$ 1.4673, $[\alpha]_D -4.3^{\circ}$. The observed exaltation in the molecular refraction (+0.49) does not enable any conclusion to be drawn between the two possible formulae. It is interesting to note the



change in the rotatory power which accompanies this isomerisation, since the *isopulegone* used in the experiments had $[\alpha]_D +34.3^{\circ}$. Since this *isopulegone* was separated from pennyroyal oil, it must be admitted that the results described would appear to support their claim for its occurrence in nature. Savard* has investigated the ultra-violet absorption spectrum of *isopulegone*; it is unfortunate that he did not examine also that of *isopulegenol* since this should distinguish between the two possible formulae.

d-isopulegoneoxime, which can be prepared from either *isopulegone* or *pulegone* (compare p. 382), melts at $120-121^{\circ}$ and is always laevorotatory ($[\alpha]_D -25.8^{\circ}$ in methyl alcohol), whether prepared from *d-pulegone* or *d-isopulegone*. The *dl-oxime* melts at $138-139^{\circ}$.

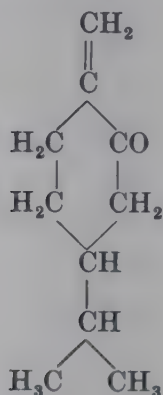
* *Compt. rend.* 1928, 186, 1738.

THE SANTOLINENONES

The essential oil from *Santolina Chamaecyparissus* L. has been shown by Francesconi and his collaborators to contain three ketones, $C_{10}H_{16}O$, designated α -, β - and γ -santolinenones. These ketones have not been obtained pure and the constitutions assigned to them must be regarded as doubtful, since they have been deduced solely from a study of their derivatives. The γ -ketone is probably dicyclic and need not be considered further here.

α -SANTOLINENONE

($\Delta^{1(7)}$ -p-Menthen-2-one or
1-Methylene-4-isopropylcyclohexan-2-one?)



It was observed by Francesconi and Scarafia* that when an alcoholic solution of the oil from *S. Chamaecyparissus* was treated with hydroxylamine hydrochloride in the presence of sodium carbonate, a mixture of products was obtained: (i) a *hydroxylamino-oxime*, (ii) two liquid *oximes* and (iii) a *hydroxylamine*. The hydroxylamino-oxime could be separated either by direct crystallisation or by distillation in steam, in which the other products were volatile.

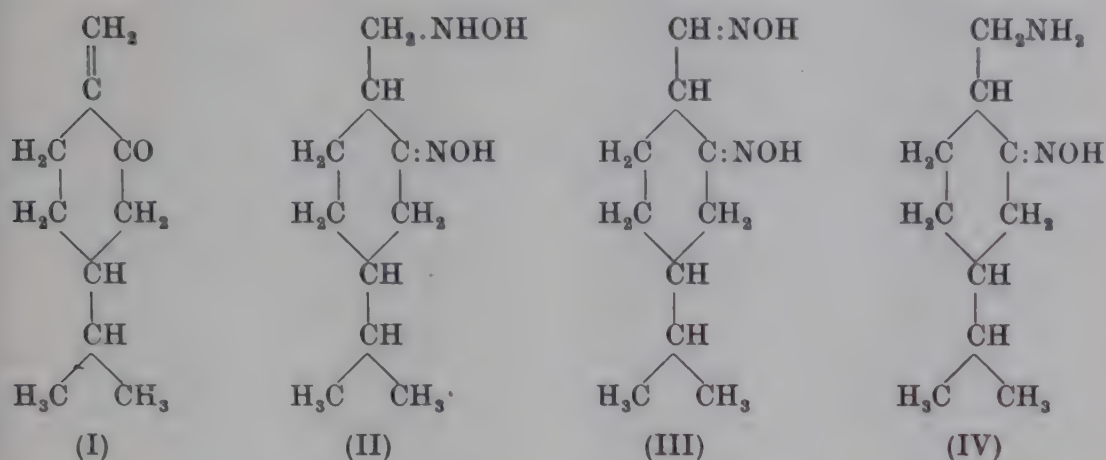
α -Santolinenone hydroxylamino-oxime[†] crystallised in prisms, m.p. 190° , but it could not be hydrolysed to the parent ketone, since on treatment with mineral acids it behaved like pulegone hydroxylamino-oxime[‡] and gave an iminonitrile (see below).

* *Atti R. Accad. Lincei*, 1911 [v], **20**, II, 318.

† Francesconi and Granata, *Gazzetta*, 1915, **45**, I, 167.

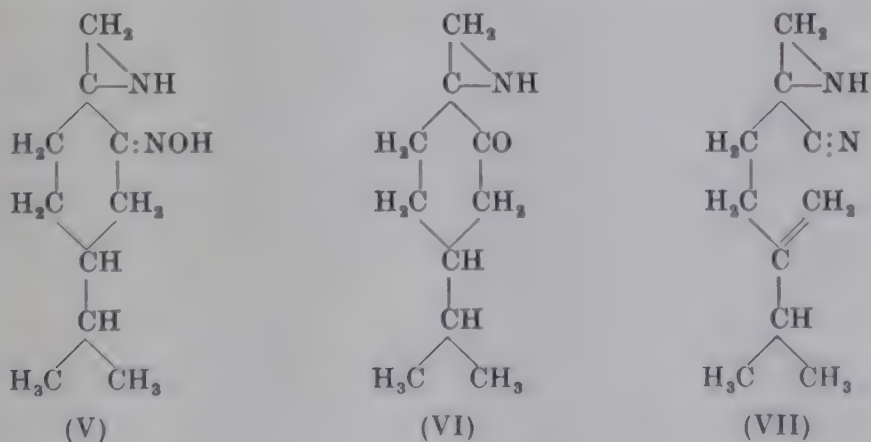
‡ Compare Francesconi and Sanna, *ibid.* 1915, **45**, I, 35.

The formation of the hydroxylamino-oxime indicates that the carbonyl group and the ethylenic linkage must be conjugated, and Francesconi and Scarafia suggested that the ketone can be represented most satisfactorily by formula (I), when the hydroxylamino-oxime would be (II).



When the hydroxylamino-oxime is heated in alcoholic solution simultaneous oxidation and reduction takes place with formation of a *dioxime* (III), m.p. 260°, and an *amino-oxime* (IV), m.p. 155°. Both substances can be prepared by heating the hydroxylamino-oxime above its melting-point, whilst the dioxime is obtained also by the action of nitrous acid on this substance.

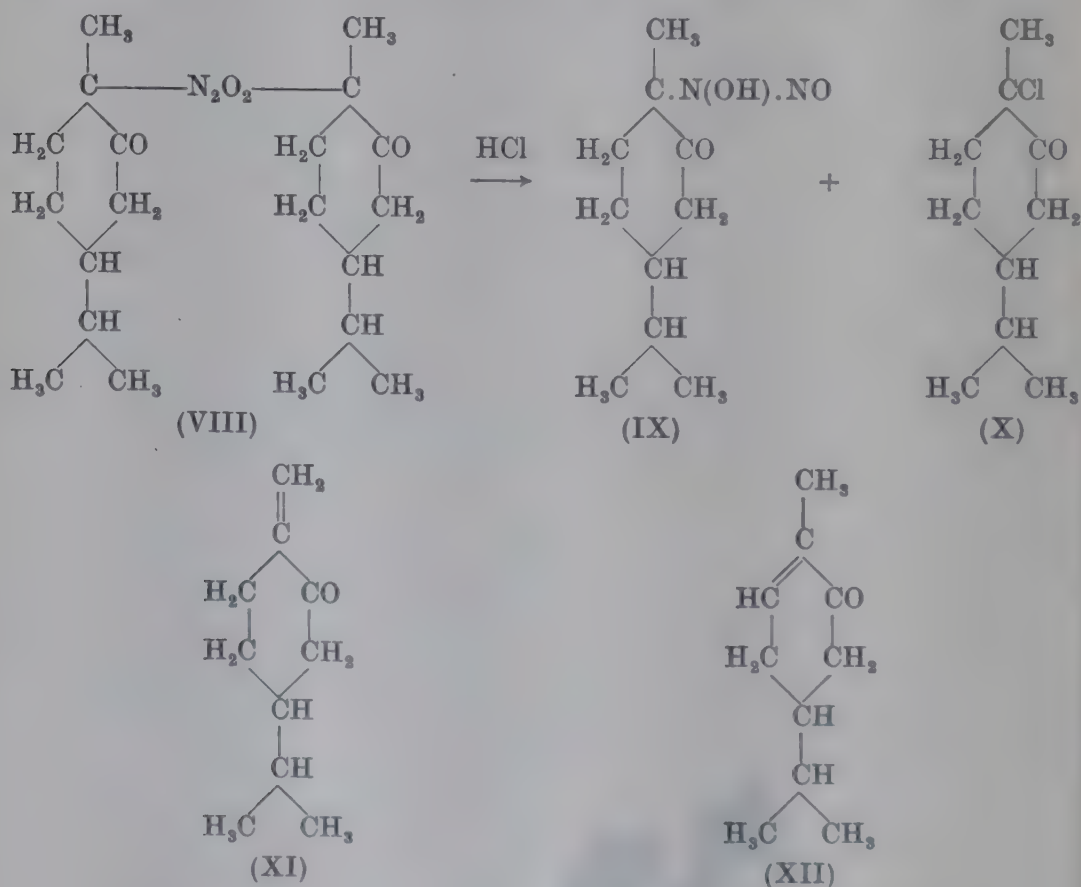
By the action of mineral acids on the hydroxylamino-oxime, α -santolinenone-imino-oxime (V), m.p. 169–172°, and α -santolinenone-anhydrohydroxylamino-oxime or α -santolinenone nitrile imine (VII), m.p. 119–120°, are formed together with α -santolinenone imine (VI), which is a yellow oil. These formulae have not been confirmed.



Although the suggested formula for α -santolinenone contains an asymmetric carbon atom, the various derivatives mentioned above are optically inactive. Francesconi and Granata* have shown that the ketone is probably a racemate, since they have resolved into its enantiomorphs the hydroxylamino-oxime by means of *d*-camphor- β -sulphonic acid.

α -Santolinenone oxime is an oil and no other derivatives of the ketone have been described.

If the formula attributed to α -santolinenone is correct the ketone should be identical with that prepared by Baeyer and Oehler† from 1-bis-nitrosocarvomenthone (VIII). On treatment with an ethereal solution of hydrogen chloride, this nitroso-body yields a mixture of *carvomenthone nitrosylic acid* (IX) and 1-chloro-*p*-menthan-2-one (X), which are readily separable by alkali. By the action of sodium acetate on the chloro-ketone, hydrogen chloride is removed with formation of a *p*-menthenone, b.p. 233–235°. This was found not to be identical with carvotan-



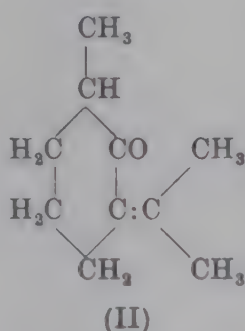
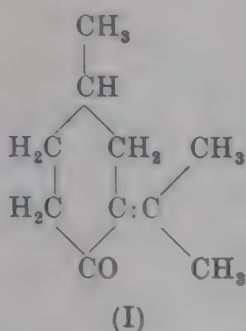
* *Gazzetta*, 1914, 44, II, 150.

† *Ber.* 1896, 29, 35.

acetone (XII) and it must therefore be $\Delta^{1(7)}$ -*p*-menthen-2-one (XI).* The semicarbazone, m.p. 222–223°, crystallised with one molecule of water of crystallisation. It would be of interest to prepare the hydroxylamino-oxime of the synthetic ketone for comparison with α -santolinenone.

β -SANTOLINENONE

($\Delta^{3(8)}$ -*m*-Menthen-4-one, 1-Methyl-3-isopropylidenecyclohexan-4-one or $\Delta^{3(8)}$ -*m*-Menthen-2-one, 1-Methyl-3-isopropylidenecyclohexan-2-one?)



It was mentioned above (p. 390) that one of the products formed by the action of hydroxylamine hydrochloride on the oil from *S. Chamaecyparissus* was a hydroxylamine, β -santolinenone hydroxylamine, which, together with the oximes, is volatile in steam and can be separated from the latter by acidification and redistillation, when the hydroxylamine alone is volatile. The hydroxylamine, m.p. 62–64°, like the majority of derivatives of this type, is very stable and cannot be hydrolysed to the parent ketone. On oxidation with mercuric oxide, it gives a nitroso-compound, m.p. 60–62°, which is blue when fused or in solution. The oxime of the ketone is described as an oil.

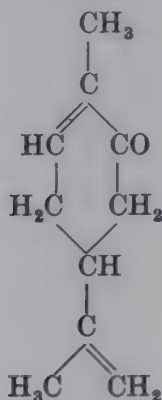
According to Francesconi and Granata,[†] β -santolinenone is best represented by either formula (I) or (II). It is, however, most improbable that either of these can be correct, since up to the present no derivatives of *m*-cymene have been found to occur in nature.

* The ketone prepared by Baeyer and Oehler was probably optically active, but no rotation is quoted.

[†] *Gazzetta*, 1916, **46**, II, 251.

CARVONE

($\Delta^{6:8(9)}$ -p-Menthadien-2-one or
1-Methyl-4-isopropenyl- Δ^6 -cyclohexen-2-one)



Carvone, $C_{10}H_{14}O$, is a common constituent of essential oils,* and has been found to occur in both the optically active and racemic forms. It is the chief ketonic constituent of dill (from the fruit of *Anethum graveolens* L.) and caraway (from the fruits of *Carum carui* L.) oils. Owing to its wide distribution, carvone has been studied from a very early date and the designation "carvol"† was given to it in 1841 by Schweizer.‡ It was probably first obtained pure by Varrentrapp,§ who made the important observation that it gave with hydrogen sulphide a crystalline derivative, from which it could be regenerated by alkali. Varrentrapp also showed that it had the empirical formula $C_{10}H_{14}O$. It may be mentioned that Schweizer had observed that it could be isomerised to carvacrol. The formation of carvone from α -pinene has been discussed by Delépine.||

The determination of the constitution of carvone is closely connected with the determination of that of limonene (dipentene) (p. 143) and the earlier investigations need only be briefly referred to here. Kekule¶ suggested that it was probably best represented by either (I) or (II), the oxide formula being preferred. It must be borne in mind in considering these formulae that, at the time when they were suggested, it was not known

* Compare Gildemeister and Hoffmann, *Die Ätherischen Öle*, 1928, I, 555.

† This was changed to carvone by Wallach, *Annalen*, 1893, 277, 116.

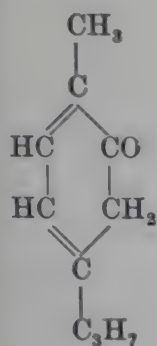
‡ *J. pr. Chem.* 1841, 24, 257.

§ *Handwörterbuch der Chemie von Liebig, Poggendorff und Wöhler*, IV, 686.

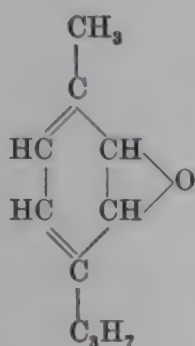
|| *Bull. Soc. chim.* 1937 [v], 4, 1669.

¶ *Ber.* 1873, 6, 933.

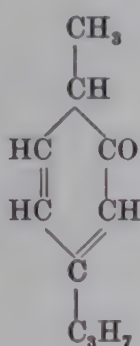
whether *p*-cymene and carvacrol contained an *n*-propyl or *iso*-propyl group. The crucial experiments on the constitution of the ketone were due to Goldschmidt and his collaborators. By the preparation in 1884 of carvoxime and carvone phenylhydrazone,* he definitely proved the presence of a carbonyl group, and shortly afterwards in collaboration with Zürrer,† he made the fundamental discovery that *carvoxime* and *nitroso-limonene* were identical (compare p. 145).



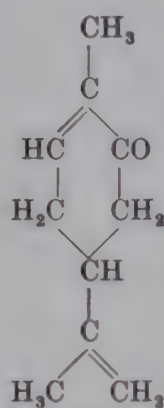
(I)



(II)



(III)



(IV)

Goldschmidt concluded from these experiments that (I) was a correct representation of the ketone, but somewhat later‡ he suggested formula (III) in order to account for its optical activity. During the ensuing years the oxidation products of the ketone were studied by numerous investigators, and in 1894 Wagner,§ in a paper correlating the chemistry of α -pinene, limonene, α -terpineol and carvone, advanced the formula (IV), which has since been proved to be correct. Although this formula did not at first receive general acceptance, since it did not account readily for the conversion of the ketone into carvacrol, the experiments of Tiemann and Semmler|| on the oxidation of dihydrocarveol (compare p. 281), which established beyond question the presence of the *isopropenyl* group, fully confirmed it.

In view of the identity of *dl*-carvoxime with nitrosodipentene the rational synthesis of the ketone follows from W. H. Perkin jun.'s synthesis of dipentene, which is described on p. 150.

* *Ber.* 1884, **17**, 1577.

‡ *Ibid.* 1887, **20**, 490.

|| *Ibid.* 1895, **28**, 2147.

† *Ibid.* 1885, **18**, 1729.

§ *Ibid.* 1894, **27**, 2270.

Carvone can be characterised either by the compound which it forms with hydrogen sulphide (p. 404) or by its *oxime* (*d*- and *l*-forms, m.p. 72–73°; *dl*-, m.p. 93°). In some cases possibly the preparation of the *phenylhydrazone-m-carboxylic acid*, m.p. 158°, described by Willstätter, Schuppli and Mayer* may prove advantageous.

Carvone is a somewhat viscid colourless oil with a highly characteristic odour. The following constants have been recorded: *d*-, b.p. 230°/755 mm., $d_4^{18.7^\circ}$ 0.9611, $n_D^{18.7^\circ}$ 1.4993, $[\alpha]_D^{20^\circ} + 62.32$; *l*-, b.p. 230–231°/763 mm., $d_{15}^{15^\circ}$ 0.9652, $n_D^{20^\circ}$ 1.4988, $[\alpha]_D^{20^\circ} - 62.46$; *dl*-, b.p. 230–231°, $d_{15}^{15^\circ}$ 0.9645, $n_D^{20^\circ}$ 1.5003. The molecular refraction shows an exaltation of +0.46, which, according to Auwers and Eisenlohr,[†] is in good agreement with the constitution of the ketone, in which there is conjugation between one of the ethylenic linkages and the carbonyl group.

The absorption spectrum in the ultra-violet has been examined by Henderson, Henderson and Heilbron[‡] and compared with the spectra of mesityl oxide and methylheptenone. As was to be expected, those of carvone and mesityl oxide show a close resemblance. In the vapour state the absorption spectrum has been studied by Purvis,[§] whilst Lowry and Abram^{||} have examined its rotatory dispersion. The Raman spectrum has been measured by Naves and Bachmann.[¶]

The action of reducing agents on carvone has been investigated very thoroughly.** It can on reduction theoretically give rise to three ketones, *dihydrocarvone* (V), *carvotanacetone* (VI) and *carvomenthone* (VII), and by the use of suitable experimental conditions the preparation of all these is possible.

Haller and Martine^{††} were responsible for the earliest experiments on the catalytic hydrogenation of the ketone, and, making use of the Sabatier-Senderens method with a nickel catalyst, they succeeded in reducing both the ethylenic linkages and the carbonyl group with the formation of a mixture of the stereoisomeric *carvomenthols*. By working under pressure with a nickel

* *Annalen*, 1919, **418**, 128.

† *J. pr. Chem.* 1910 [ii], **82**, 136.

‡ *Ber.* 1914, **47**, 883; compare Cooke and Macbeth, *J.C.S.* 1938, p. 1408.

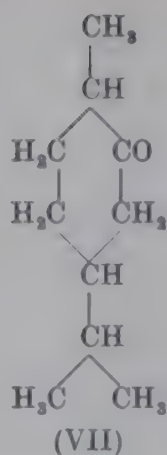
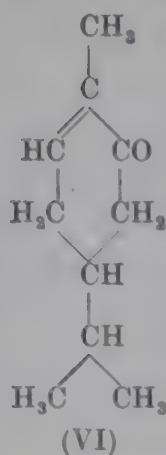
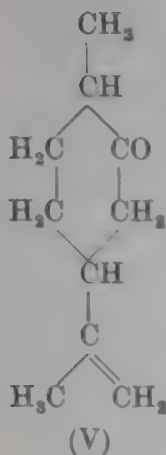
§ *J.C.S.* 1923, **123**, 2518.

|| *Ibid.* 1919, **115**, 309.

¶ *Helv. Chim. Acta*, 1946, **29**, 61.

** Compare Nagasawa, *J. Soc. Chem. Ind. Japan*, 1938, **41**, Supp. binding, p. 252.

†† *Compt. rend.* 1905, **140**, 1302.



oxide catalyst, Ipatiev and Balatschinsky* found that at 280° and 120 atmospheres carvomenthol was formed, whilst at 220 – 240° only the ethylenic linkages were reduced and *carvomenthone* was obtained; more recently, it has been shown that this ketone may be prepared in excellent yield by the use of a palladium-calcium carbonate catalyst.† Vavon‡ investigated exhaustively the conditions governing the hydrogenation of *d*-carvone in the presence of platinum black, and he showed that by suitably regulating the supply of hydrogen it is possible to prepare either *d*-carvotanacetone, *l*-carvomenthone or *l*-carvomenthol. For complete hydrogenation to the alcohol a very active catalyst is required. It is interesting to note that dihydrocarvone cannot be prepared by the catalytic hydrogenation of carvone, but, if the reduction is carried out electrolytically in acid solution, this ketone is formed, although in alkaline media the main products are the pinacones, α - and β -dicarvelones.§

By the use of aluminium isopropoxide, Johnston and Read|| have reduced both *d*- and *l*-carvone to the corresponding *carveols*. With sodium and alcohol,¶ carvone is reduced to the alcohol, dihydrocarveol, whilst with zinc dust in sodium hydroxide or acetic acid solution** the corresponding ketone, *dihydrocarvone*, is obtained. The formation of dihydrocarvone is always accompanied by reduction to the pinacone, α -dicarvelone, $\text{C}_{20}\text{H}_{30}\text{O}_2$ (*d*- and *l*-forms, m.p. 148 – 149° ; *dl*-, m.p. 120 – 121°), which has

* Ber. 1911, **44**, 3461.

† Read and Johnston, *J.C.S.* 1934, p. 229; compare Dulou, *Bull. Inst. Pin*, 1934, p. 173.

‡ *Compt. rend.* 1911, **153**, 68; compare Wallach, *Annalen*, 1911, **381**, 69.

§ Law, *J.C.S.* 1912, **101**, 1027, 1549.

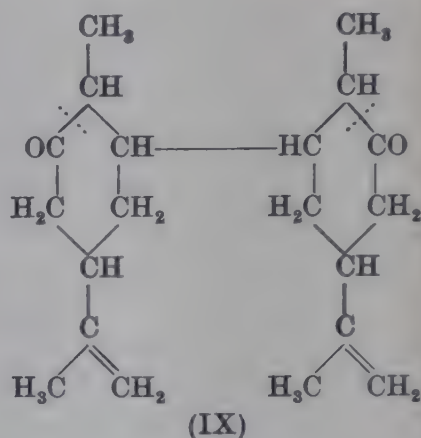
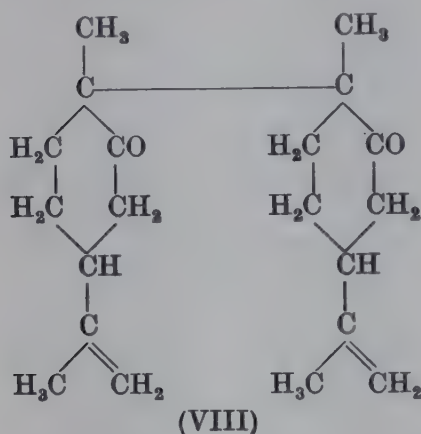
|| *Ibid.* 1934, p. 233.

¶ Wallach, *Annalen*, 1893, **275**, 111.

** Wallach, *ibid.* 1894, **279**, 377.

an optical rotation opposite in sign to the parent ketone. The properties of the pinacone were investigated by Wallach,* who was successful in determining its constitution.

α -Dicarvelone reacts with hydrogen bromide to yield a *dihydrobromide*, which on treatment with alkali, gives an isomeric pinacone, β -dicarvelone (*d*- and *l*-forms, m.p. 206–207°; *dl*-, m.p. 168°), whilst both α - and β -dicarvelones are isomerised by concentrated sulphuric acid to γ -dicarvelone (*d*- and *l*-forms, m.p. 126°; *dl*-, m.p. 112°). The α -pinacone can be represented by either formula (VIII) or (IX).



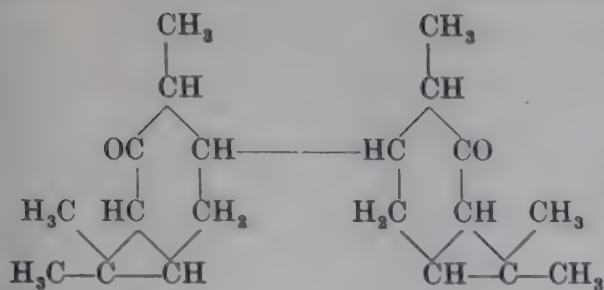
On catalytic hydrogenation two molecules of hydrogen are taken up with the formation of *tetrahydro- α -dicarvelone*, m.p. 129–130°, which, when oxidised with chromic acid, yields a ketonic acid, and this on treatment with sodium hypobromite gives bromoform. It is probable, therefore, that the pinacone is represented by (IX), since, on oxidation of the saturated derivative, fission would occur at the positions indicated by the dotted lines, to yield an acid containing two CH_3CO groups.

The β -pinacone is most probably the tetracyclic body (X), since it cannot be hydrogenated catalytically; the γ -pinacone, on the other hand, gives on reduction the same tetrahydropinacone as α -dicarvelone and it is therefore undoubtedly the corresponding “carvenone” derivative (XI).

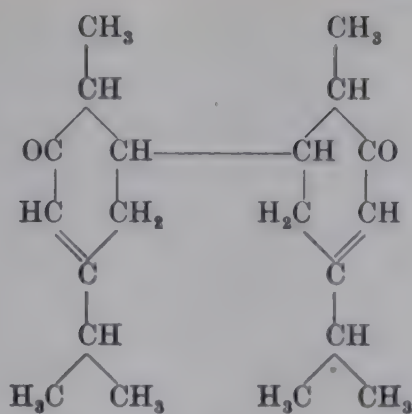
Carvone is attacked somewhat readily by oxidising agents. When it is shaken with air or oxygen in the presence of baryta water, it yields according to Harries† a yellow diketone identical with that obtained by the hydrolysis of carvonedioxime (see

* *Annalen*, 1914, 403, 79.

† *Ber.* 1901, 34, 2105.



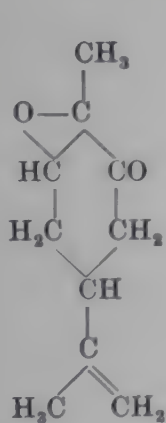
(X)



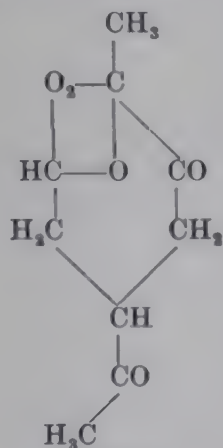
(XI)

p. 407). On exposure of a water-alcohol solution of the ketone to sunlight, it was found by Ciamician and Silber* to isomerise with formation of a crystalline ketone, designated *camphor-carvone*. According to Sernagiotto,[†] this ketone is tricyclic, but sufficient evidence is not available for its constitution to be discussed. Autoxidation of carvone, and also its reaction with hydrogen peroxide, have been studied by Treibs,[‡] the main product being the oxide (XII).

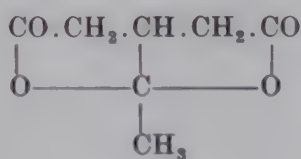
By oxidation of carvone with ozone, Harries and Neresheimer[§] obtained an oily *diozonide*, which on further treatment with ozone was converted into a *peroxide*. This unstable peroxide decomposed explosively to yield a *diketo-ozonide*, probably represented by (XIII), from which, by the action of steam, the *ketodilactone* (XIV) of β -acetylglutaric acid was obtained.



(XII)



(XIII)



(XIV)

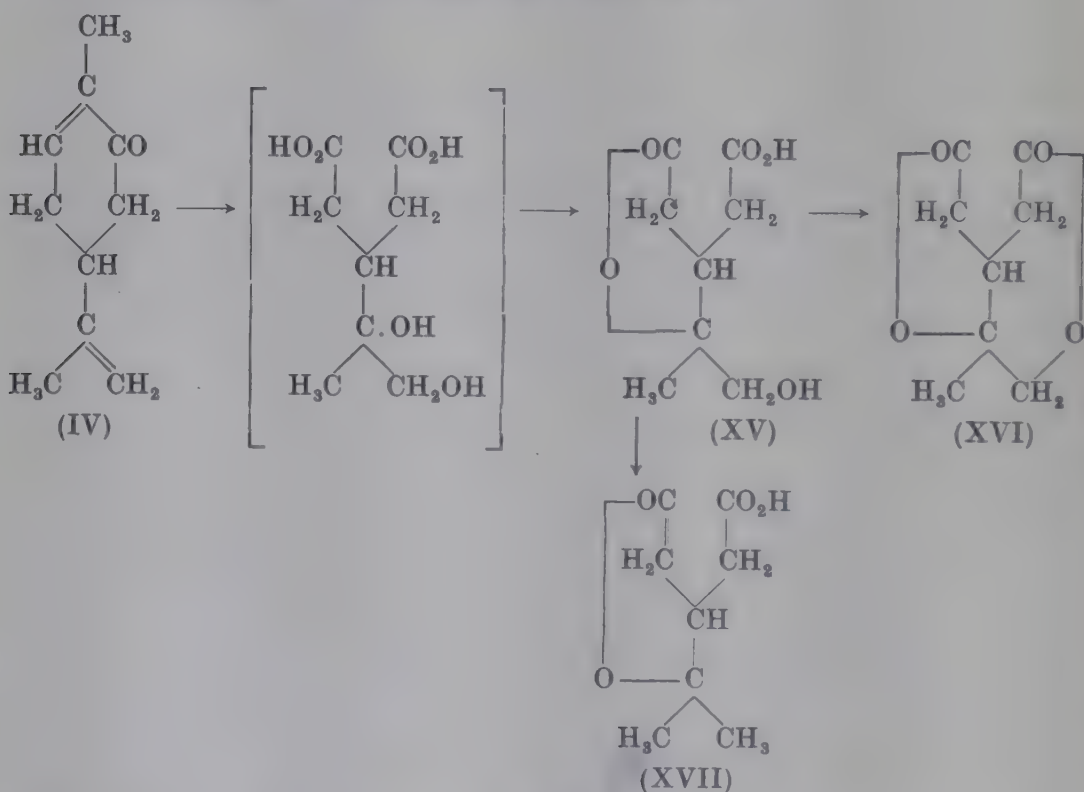
* Ber. 1908, **41**, 1931.

[†] Atti R. Accad. Lincei, 1914 [v], **23**, II, 70; Gazzetta, 1918, **48**, I, 52.

[‡] Ber. 1931, **64**, 2178; 1932, **65**, 1314; 1933, **66**, 1484.

[§] J.C.S. Abs. 1917, **112**, I, 212.

The oxidation of carvone with potassium permanganate was investigated simultaneously by Best* and Wallach.† As was to be anticipated with a substance containing two ethylenic linkages, the degradation is profound, and much difficulty was experienced in the determination of the constitution of the substances formed. A correct interpretation of the results only became possible after Tiemann and Semmler‡ had investigated the oxidation of dihydrocarveol. It will be observed that carvone and limonene give rise to the same oxidation products (compare p. 156). The main product of the oxidation is a *hydroxy acid*, $C_8H_{12}O_5$, m.p. $190-192^\circ$, which was shown to be *hydroxy-terpenylic acid* (XV), since, on reduction with hydriodic acid, it gave *terpenylic acid* (XVII), whilst on distillation under diminished pressure, it was converted into the *dilactone* (XVI), m.p. 129° . The formation of these products will be readily understood from the scheme set out below.



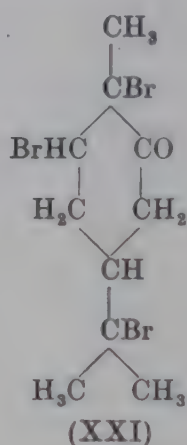
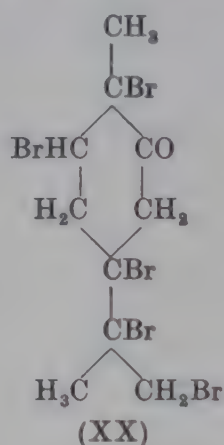
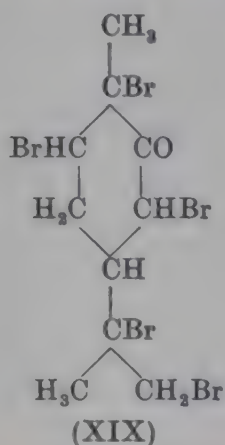
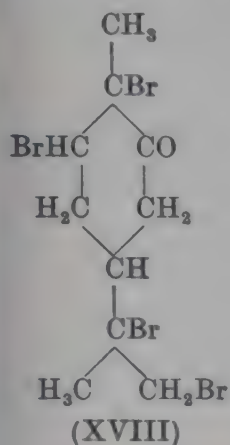
Bromination of carvone leads to a mixture of crystalline (*d*- and *l*-forms, m.p. $120-122^\circ$; *dl*-, m.p. $112-114^\circ$) and liquid

* Ber. 1894, 27, 1218, 3333.

† Annalen, 1893, 275, 155; Ber. 1894, 27, 1495.

‡ Ber. 1895, 28, 2148.

tetrabromides, which were investigated by Wallach.* These tetrabromides are probably stereoisomerides, represented by (XVIII). On further bromination, the crystalline tetrabromide yields a *pentabromide* (*d*- and *l*-forms, m.p. 86–87°; *dl*-, m.p. 96–98°), whilst the liquid bromide yields an isomeric *pentabromide* (*d*- and *l*-forms, m.p. 142–143°; *dl*-, m.p. 124–126°). These pentabromides are similarly probably stereoisomerides of the formula (XIX). Direct proof of the position of the fifth halogen atom is not available, but the formula suggested below appears to the writers to be more probable than that (XX) suggested by Semmler.†



Carvone tribromide (XXI) can be prepared by the bromination of the ketone in acetic acid solution containing hydrogen bromide;‡ the optically active forms of the bromide are oils, but the *dl*-form melts at 74–76°. The action of alkalis on this bromide was studied by Wallach and his collaborators,§ who showed that *cyclopentene* derivatives are formed. These interesting substances, however, cannot be considered here.

All the halogen derivatives of carvone can be reconverted into the parent ketone by reduction with zinc in acetic acid solution.

With hydrogen chloride in acetic acid solution, carvone yields a *monohydrochloride*,|| which on warming, especially in the presence of catalysts, passes into carvacrol. Carvone monohydrochloride is an oil, but it yields a crystalline *oxime* (*d*- and *l*-forms, m.p. 135–136.5°; *dl*-, m.p. 127–128°), a substance prepared more

* *Annalen*, 1894, **279**, 390; 1895, **286**, 120.

† *Die Ätherischen Öle*, 1906, Vol. III, 723.

‡ Wallach, *Annalen*, 1895, **286**, 119.

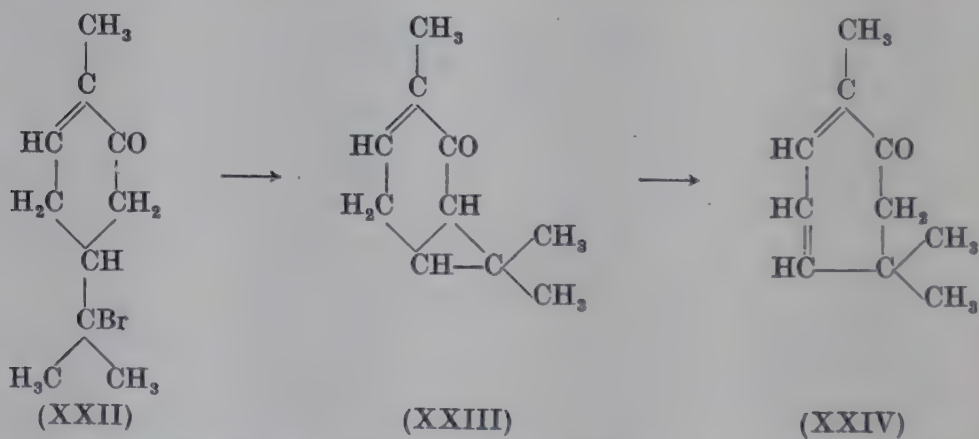
§ *Ibid.* 1899, **305**, 245; 1918, **414**, 240.

Goldschmidt and Kisser, *Ber.* 1887, **20**, 488; Wallach, *Annalen*, 1899, **305**, 235.

readily by the action of hydrogen chloride on carvoxime.* The oxime hydrochloride is formed also by the action of hydrogen chloride on α - and β -limonene nitrosochlorides.

Carvone reacts in a similar manner with hydrogen bromide, yielding *d*-carvone hydrobromide, melting according to Baeyer[†] at 32°. With hydroxylamine, it yields an *oxime*, which can be prepared also by the action of hydrogen bromide on carvoxime. There would appear to be some doubt as to the correct melting-point of this derivative; according to Baeyer[‡] the *d*-form melts at 133–134° or 136°, whilst Goldschmidt and Kisser[§] and Wallach and Lautsch^{||} stated that it melts at 116°. It is possible that these are the melting-points of the *syn*- and *anti*-forms of the oxime. The *dl*-form melts at 127–128°.

Reduction of carvone hydrobromide with zinc dust in an alcoholic solution yields carvotanacetone, but if the hydrobromide (XXII) is treated with an alcoholic solution of potassium hydroxide, it was observed by Baeyer[¶] to undergo a remarkable reaction, being converted into the *cycloheptadiene* ketone, *eucarvone* (XXIV). The formation of this ketone takes place probably with the intermediate formation of the dicyclic ketone (XXIII).



The constitution of eucarvone was established by the investigations of Baeyer and Wallach;** further reference will be made to the chemistry of this substance in considering the chemistry of carone (vol. II).

* Goldschmidt and Zürrer, *Ber.* 1885, **18**, 1731; Baeyer, *ibid.* 1896, **29**, 19; Wallach, *Annalen*, 1892, **270**, 178.

† *Ber.* 1894, **27**, 811.

‡ *Ibid.* 1887, **20**, 2072.

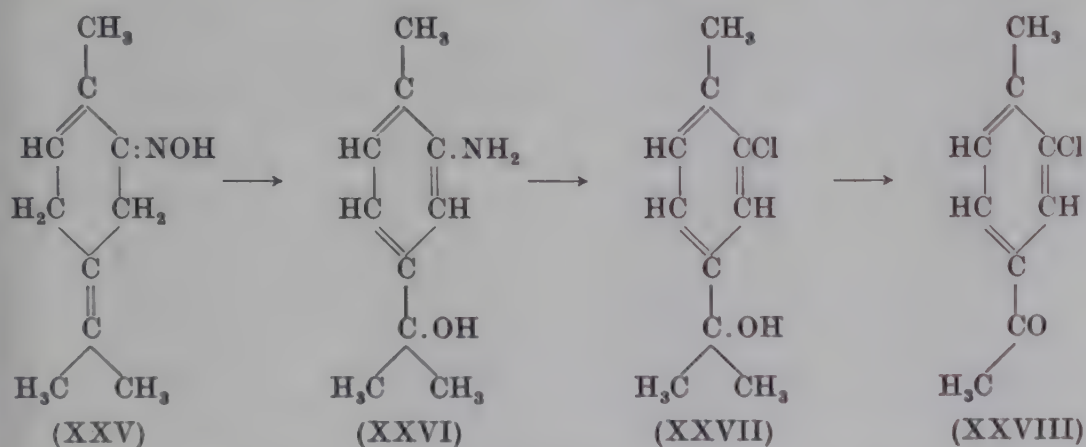
§ *Ber.* 1894, **27**, 812.

Ibid. 1894, **27**, 811; 1896, **29**, 31.

|| *Annalen*, 1906, **346**, 276.

** *Inter al.*, *Annalen*, 1905, **339**, 97.

By the action of hydroxylamine on carvone hydrobromide, Goldschmidt and Kisser* prepared an isomeride of carvoxime, *isocarvoxime*, m.p. 142–143°. It was subsequently observed that this substance could be prepared also by the action of either potassium hydroxide or hydroxylamine on carvoxime hydrobromide (or hydrochloride) and that it was reconverted into this substance by treatment with the halogen acid: The investigations of Baeyer† and of Wallach‡ have shown conclusively that it is the *oxime* of $\Delta^{1:4(8)}$ -*p-menthadiene-6-one* (XXV). When the oxime is digested with a dilute solution of oxalic acid it yields, in addition to carvacrol, a base, *carvoline*, m.p. 94°. Carvoline is an aromatic base and has the formula (XXVI). By the Sandmeyer reaction it can be converted into the *hydroxychloride* (XXVII), from which, by oxidation with chromic acid, the *p-acetyl-o-chlorotoluene* (XXVIII), m.p. 45–46°, can be prepared.



Mention has been made already of the great ease with which carvone can be isomerised to carvacrol, a change which can be effected with nearly all dehydrating agents, and also with palladium.§ The hydration of the ketone was first carried out by Rupe and Schlochoff,|| who found that when *d*-carvone was shaken with sulphuric acid (40 per cent.), *hydroxycarvotanacetone* (XXIX), m.p. 41–42°, $[\alpha]_D + 43.0^\circ$ (semicarbazone, m.p. 176°), was formed. This substance was also obtained by Knoevenagel and Samel¶ by digesting an aqueous solution of the sodium

* Ber. 1887, 20, 2073.

† Ibid. 1896, 29, 12.

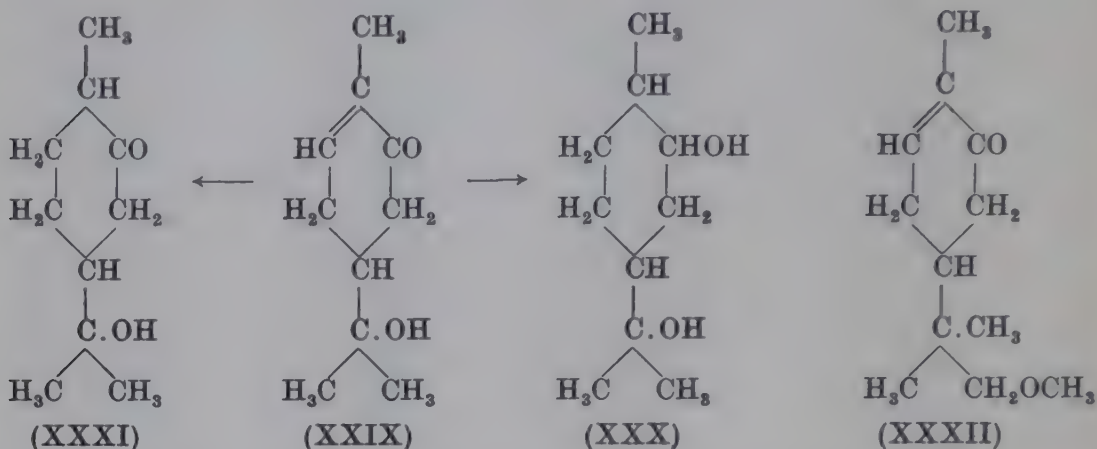
‡ Annalen, 1906, 346, 277.

§ Linstead, Michaelis and Thomas, J.C.S. 1940, p. 1139.

|| Ber. 1905, 38, 1719.

¶ Ibid. 1906, 39, 677.

salt of the bisulphite derivative of carvone until complete conversion into the sulphonic acid had taken place. Treatment of the sulphonic acid with sulphuric acid gave hydroxycarvotanacetone.



The constitution of the hydroxy-ketone was proved by its reduction to *p*-menthane-2:8-diol (XXX), m.p. 112–113°, identical with the glycol prepared by Baeyer and Henrich* from dihydrocarveol hydrobromide. Reduction with zinc dust in alcoholic solution yields *hydroxycarvomenthone* (XXXI), b.p. 135–139°/9 mm.†

Treibs‡ has shown that the exocyclic ethylenic linkage in carvone reacts in an unusual manner with methanolic sulphuric acid to give the compound (XXXII) (compare p. 354).

Attention has been directed already to the compound which carvone forms with hydrogen sulphide as a valuable means for the separation and identification of the ketone. This derivative is prepared most readily by the method devised by Wallach,§ namely, by passing hydrogen sulphide into an alcoholic solution of the ketone containing ammonia. There is some doubt as to the correct melting-point of the *d*- and *l*-forms of this substance. According to Harries,|| these melt at 224–225°, but Deussen¶ and also Hooper, Macbeth and Price** have found the melting-point to be 210–211° ($[\alpha]_D + 49.2^\circ$, -48.1° in chloroform); the

* Ber. 1895, 28, 1589.

† Compare Baeyer and Henrich, *ibid.* p. 1590.

‡ Ber. 1937, 70, 386.

§ Annalen, 1899, 305, 224.

|| Ber. 1901, 34, 1928; see also Dulou, *Bull. Inst. Pin.*, 1934, p. 205; Padmanabhan, *Current Sci.* 1935, 4, 95.

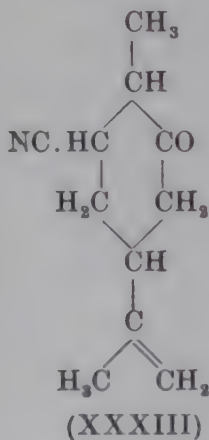
¶ J. pr. Chem. 1914 [ii], 90, 318.

** J.C.S. 1934, p. 1147.

dl-form melts at 189–190°. The pure ketone can be regenerated from the hydrogen sulphide compound by digestion with alkali.

When carvone is shaken with a solution of sodium bisulphite, it forms the sodium salt of a *disulphonic acid*, $C_{10}H_{16}O_7S_2Na_2$, addition taking place at both of the ethylenic linkages;* with a dilute solution of sulphur dioxide, however, Knoevenagel† prepared a *mono-derivative*, the sodium salt, $C_{10}H_{15}O_4SNa$, of which was isolated.

The addition of hydrogen cyanide to *d*-carvone was investigated by Lapworth,‡ who showed that *cyanodihydrocarvone* (XXXIII), m.p. 93–94.5°, $[\alpha]_D + 13.5^\circ$, is formed. In this reaction a new asymmetric centre is introduced and the nitrile shows mutarotation in solution. From this mononitrile a *dinitrile*, m.p. 104–108°, $[\alpha]_D + 11.5^\circ$, can be prepared, but it is unstable and readily loses hydrogen cyanide. By working under somewhat different conditions Lapworth and Steele§ obtained a second mononitrile, *neocyanodihydrocarvone*, m.p. 84°, $[\alpha]_D - 39^\circ$, which, like its isomeride, shows mutarotation.



From *d*-carvone Rupe and Dorschky|| prepared two *semi-carbazones*, m.p. 162–163° and m.p. 141–142°. The lower melting isomeride is however unstable, passing into the other form on keeping or on heating to 170–175°. In the case of *l*-carvone only the stable form of the semicarbazone has been prepared; the *dl*-semicarbazone melts at 154–156°.

* Labbé, *Bull. Soc. chim.* 1900 [iii], 23, 280; compare Dupont and Labaune, *Sci. Ind. Rep. Roure-Bertrand Fils*, 1913 [iii], 7, 3.

† *Ber.* 1904, 37, 4041.

§ *Ibid.* 1911, 99, 1877.

‡ *J.C.S.* 1906, 89, 945, 1819.

|| *Ber.* 1906, 39, 2113, 2372.

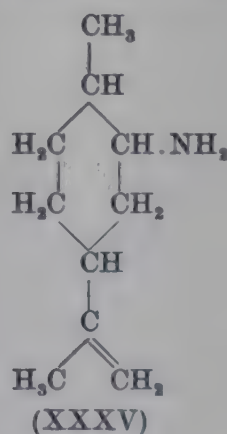
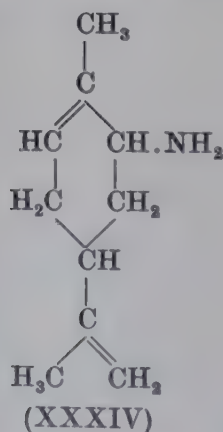
The *hydrazone* of *d*-carvone, which is an oil, was prepared by Kishner* and, when heated with potassium hydroxide, it yields limonene.† The *phenylhydrazone* melts, according to Baeyer,‡ at 109–110°, and the 2:4-dinitrophenylhydrazone at 191°.§

Owing to their importance in the development of terpene chemistry, the carvoximes have been very thoroughly investigated. *d*-Carvoxime, m.p. 71°, $[\alpha]_D + 43.9^\circ$ (in alcohol), first isolated by Goldschmidt,|| is most conveniently prepared by treating *d*-carvone with hydroxylamine hydrochloride in methyl alcoholic solution.¶ It is formed also by the action of an alcoholic solution of potassium hydroxide on either α - or β -*l*-limonene nitrosochlorides.** Deussen and Hahn†† showed that, when the nitrosochlorides are treated with sodium ethoxide, in addition to the normal oxime, a second, β -oxime, m.p. 56–57°, is formed.

l-Carvoxime has similar properties to *d*-carvoxime and in this case also a β -oxime, m.p. 58°, $[\alpha]_D + 68.3^\circ$, has been prepared from *d*-limonene nitrosochloride.

dl-Carvoxime, which melts at 92–93°, can be obtained either from carvone or by digestion of the active oximes with alcohol or ligroin, when racemisation occurs.

Goldschmidt and his collaborators** showed that when *d*- or *l*-carvoximes are reduced with sodium amalgam only the oximino group is attacked with formation of the base, *carvylamine* (XXXIV). In this reaction a new asymmetric carbon



* *J. Russ. Phys. Chem. Soc.* 1912, **44**, 1754.

† The semicarbazone behaves similarly. (Naves and Bachmann, *Helv. Chim. Acta*, 1946, **29**, 61.)

‡ Hooper, Macbeth and Price, *J.C.S.* 1934, p. 1147.

§ Harries, *Annalen*, 1903, **328**, 322.

¶ *Ber.* 1910, **43**, 519.

‡ *Ber.* 1894, **27**, 810.

|| *Ber.* 1884, **17**, 1577.

** Wallach, *Annalen*, 1892, **270**, 175.

†† *Ibid.* 1887, **20**, 486; 1893, **26**, 2084; 1897, **30**, 2069.

atom is introduced into the molecule and the existence of four active and two externally compensated forms is possible, all of which have been prepared and identified by their crystalline *benzoyl* derivatives.

With sodium and alcohol as the reducing agent,* one of the ethylenic linkages also undergoes hydrogenation with formation of dihydrocarvylamine (XXXV), which can be prepared also by the reduction of dihydrocarvoxime (p. 358).

Electrolytic reduction of carvoxime was found by Rupe and Löffl† to yield dihydrocarvoxime, whilst its catalytic hydrogenation with a palladium catalyst was investigated by Wallach.‡ Normally, carvomenthone oxime is the main product of the reaction, but by a suitable modification of the conditions carvotanacetoxime can be obtained in excellent yield.

In ethereal solution, carvoxime yields with hydrogen chloride (or bromide) salts, which are unstable and are dissociated by water; in alcoholic or acetic acid solution, addition of the halogen acid at the 8(9) ethylenic linkage occurs. By the bromination of carvoxime Deussen§ prepared a *tribromide* (*d*- and *l*-forms, m.p. 119–120°; *dl*-, m.p. 128°) and a *tetrabromide* (*d*- and *l*-forms, m.p. 126–127°; *dl*-, m.p. 121·5°. Carvoxime is extremely resistant to the action of acetic anhydride, and gives only traces of carvacrylamine.||

Carvone hydroxylamino-oxime (XXXVI) was prepared by Harries and his collaborators¶ by treatment of the ketone with an excess of hydroxylamine hydrochloride. It is an oil, which can be distilled in small quantities without decomposition, b.p. 190°/6 mm.; it slowly crystallises but the melting-point is not sharp. On oxidation with mercuric oxide, it is converted into the *dioxime* (XXXVII), m.p. 152–153°, from which, by hydrolysis, the *diketone* (XXXVIII) can be prepared, the latter being identical with that formed by the oxidation of carvone in the presence of alkali (compare p. 398).

* Wallach, *Annalen*, 1893, 275, 118.

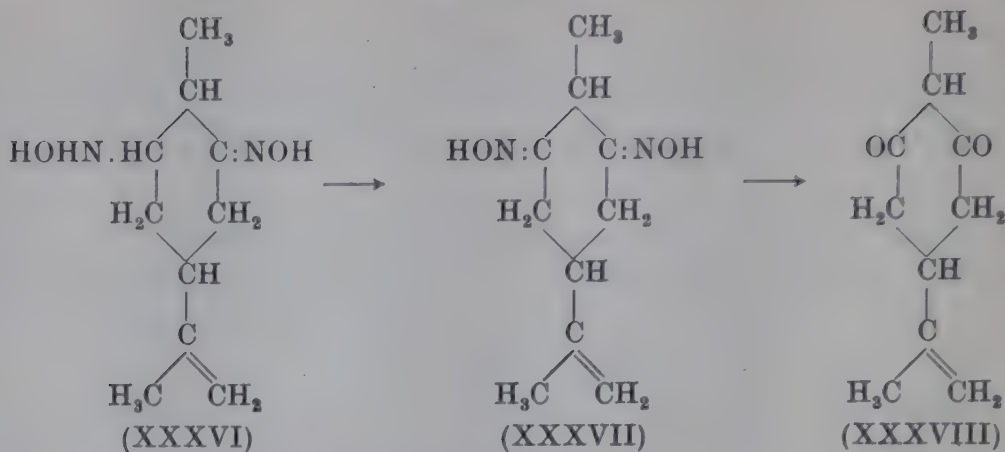
† Ber. 1914, 47, 2151.

‡ *Annalen*, 1914, 403, 73.

§ *J. pr. Chem.* 1914 [ii], 90, 318.

|| Cooke and Macbeth, *J.C.S.* 1937, p. 1593.

¶ Ber. 1898, 31, 1384, 1810; 1899, 32, 1319, 1345; *Annalen*, 1904, 330, 185; compare Wallach, *Annalen*, 1894, 279, 367.



According to Müller,* *d*-benzylidene-carvone exists in two forms, the α -form being an oil, b.p. 191–193°/10 mm., and the β -a crystalline solid, m.p. 114–115°. More recently, an amorphous dibenzylidene compound has been described by Christ and Fuson.†

A large number of reactions involving the carbonyl group have been carried out with carvone, but few of these have any particular bearing on terpene chemistry and cannot therefore be considered here. Mention need only be made of the action of *iso*amyl magnesium iodide on the ketone, which according to Semmler, Jonas and Roenisch,‡ gives an alcohol, which on elimination of water is converted into a monocyclic *sesquiterpene*, $\text{C}_{15}\text{H}_{24}$, b.p. 130–132°/11 mm., d^{20}_D 0.8679, n^{20}_D 1.4947, $[\alpha]_D +18.3^\circ$. It is also of interest that the *enol* of carvone has been obtained§ by the action of ethyl magnesium bromide on the ketone.

* Ber. 1921, 54, 1471; compare Maxim, Zugravescu and Teodorescu, Chem. Abs. 1944, 38, 5496.

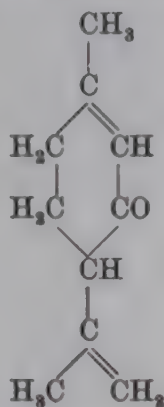
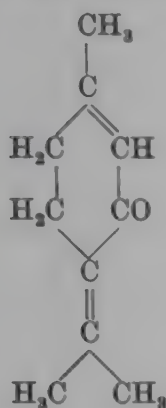
† J. Amer. C.S. 1937, 59, 896.

* Ber. 1917, 50, 1833.

‡ Grignard and Blanchon, Bull. Soc. chim. 1931 [iv], 49, 23.

PIPERITENONE AND ISOPIPERITENONE

($\Delta^{1:4(8)}$ -p-Menthadien-3-one and $\Delta^{1:8(9)}$ -p-Menthadien-3-one)



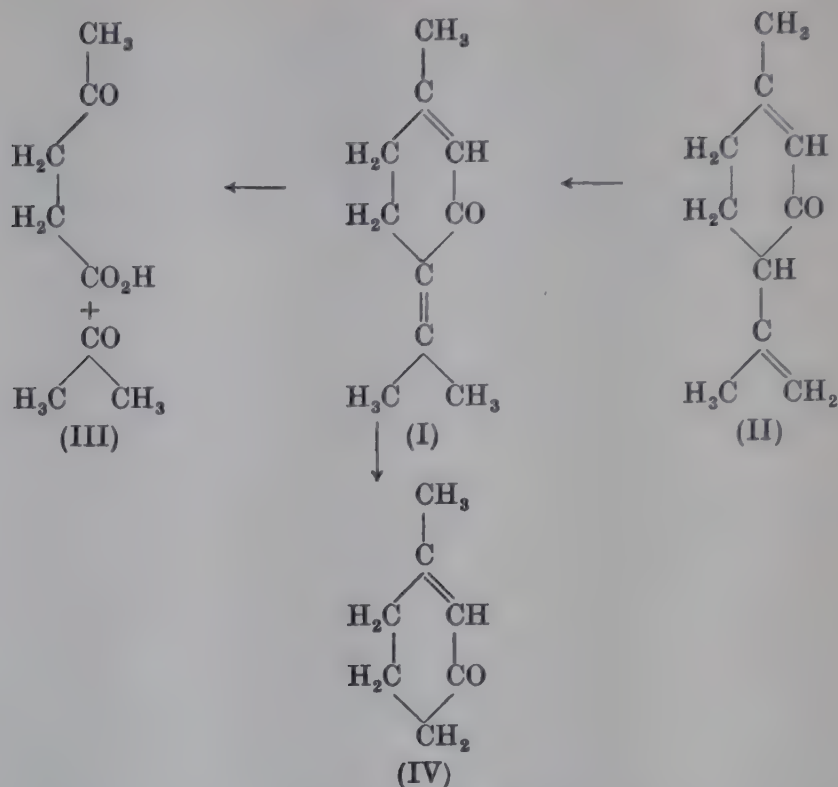
Naves* isolated from the essential oil obtained from *Mentha Pulegium* var. *Villona* Benth. from North Africa a mixture of two isomeric ketones, $C_{10}H_{14}O$, *piperitenone* (I) and *isopiperitenone* (II), the former ketone predominating and forming approximately 85 per cent. of the mixture. The structure of these two ketones was comparatively readily determined. On ozonolysis, acetone, formaldehyde and levulinic acid (III) were obtained, the acetone and levulinic acid resulting from the degradation of piperitenone (I), whilst *isopiperitenone* (II) present gave formaldehyde. Further proof of the presence of (I) was obtained by digestion of the mixture of ketones with formic acid, when acetone and *methyl- Δ^1 -cyclohexen-3-one* (IV) were obtained, the scission being similar to that occurring with pulegone (compare p. 371).

Although the only direct evidence of the presence of *isopiperitenone* is the formation of formaldehyde on ozonolysis, indirect evidence is afforded by (i) the optical activity of the ketones, (ii) the fact that, on digestion with sodium ethoxide, pure piperitenone is formed,[†] and (iii) the Raman spectrum indication of the presence of an *isopropenyl* group.

The mixture of ketones was an oil having an odour resembling that of pulegone, although somewhat less pleasant. It had b.p. $97^\circ/2.5$ mm., d_4^{20} 0.9738–0.9742, n_D^{20} 1.5284–1.5288, α_D -2.16° to -2.28° (2:4-dinitrophenylhydrazone, m.p. 184.5°).

* *Helv. Chim. Acta*, 1942, **25**, 732.

† Naves and Papazian, *Helv. Chim. Acta*, 1942, **25**, 1033.



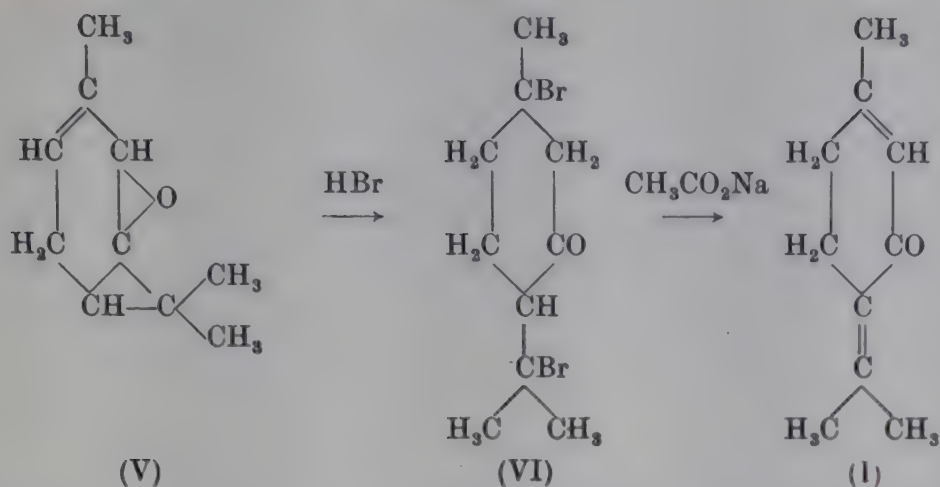
Naves and Papazian obtained piperitenone containing only traces of *isopiperitenone* by the decomposition with alkali of the compound which the former ketone gives with sodium sulphite. The ketone, purified in this manner, had b.p. $92^{\circ}/1.8$ mm., $d_4^{20^{\circ}} 0.9774$, $n_D^{20^{\circ}} 1.5294$, $\alpha_D \pm 0^{\circ}$. The absorption spectrum and other physical constants have been recorded by Naves and Papazian.*

As would be anticipated, piperitenone and *isopiperitenone* isomerise readily to thymol, the isomerisation being practically quantitative when the ketones are digested with palladium-charcoal for 3 hours. On catalytic hydrogenation, using a Raney nickel catalyst, the main product is *isomenthone*, menthone and thymol being formed in small amounts. If hydrogenated in the presence of platinum (Adams) a quantitative yield of menthols, mainly *isomenthol*, is obtained.

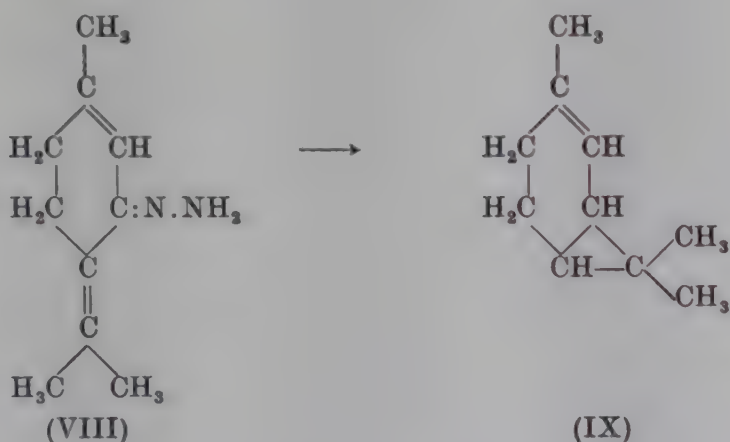
Prior to its isolation from *Mentha Pulegium*, piperitenone (I), then termed $\Delta^{1:4(8)}$ -*p-menthadiene-3-one*, was prepared by Penfold, Ramage and Simonsen[†] by the action of sodium acetate on 1:8-dibromo-*p-menthan-3-one* (VI) formed by the action of hydrogen bromide on 1- Δ^3 -*caren-5:6-epoxide* (V).

* *Loc. cit.* pp. 1023, 1046.

† *J.C.S.* 1939, p. 1496.

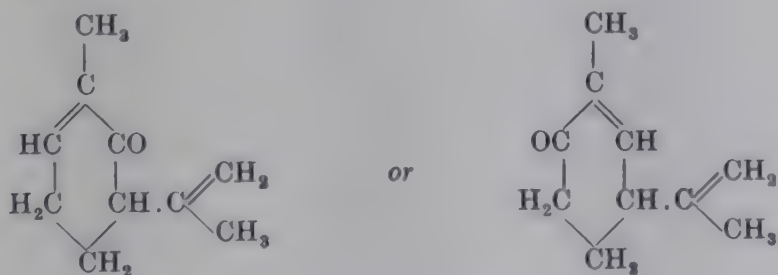


This conversion of a carene derivative into piperitenone lends additional interest to the synthesis of *dl*- Δ^4 -carene (IX) which Naves* carried out by subjecting *piperitenone hydrazone* (VIII) to the Kishner reaction.



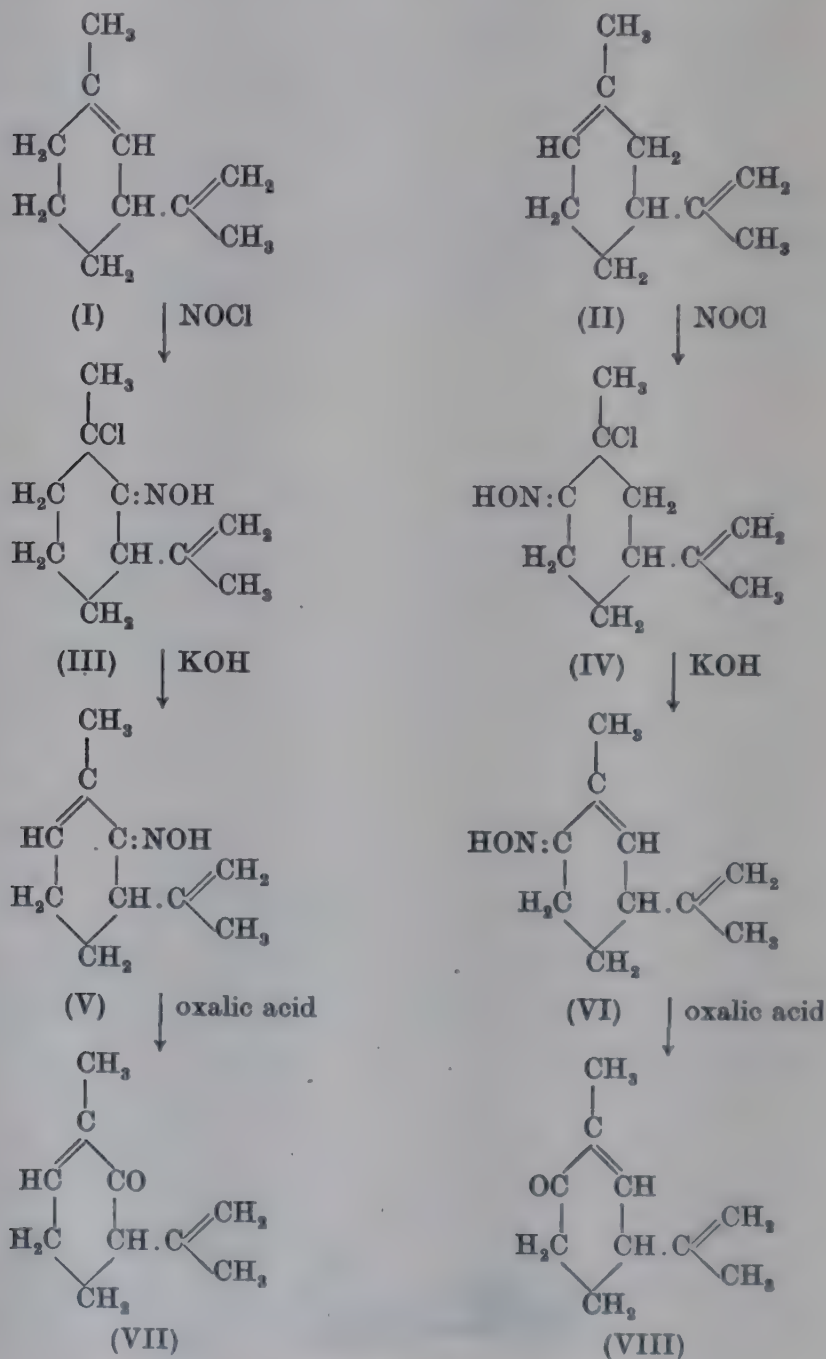
SYLVECARVONE

(^{6:8(9)}-*m*-Menthadien-2-one, 1-Methyl-3-isopropenyl- Δ^6 -cyclohexen-2-one or $\Delta^{1:8(9)}$ -*m*-Menthadien-6-one, 1-Methyl-3-isopropenyl- Δ^1 -cyclohexen-6-one)



* *Loc. cit.* p. 744; compare Naves and Papazian, *loc. cit.* p. 984.

Sylvecarvone, $C_{10}H_{14}O$, was prepared by Wallach* by the action of alkali on sylvestrene nitrosochloride, when the liquid *oxime* (V) or (VI) was obtained, which on hydrolysis with oxalic acid gave the parent ketone. Owing to the limited quantity of material available, it could not be purified. The *semicarbazone*, which crystallised from methyl alcohol in needles, melted at $175-177^{\circ}$.

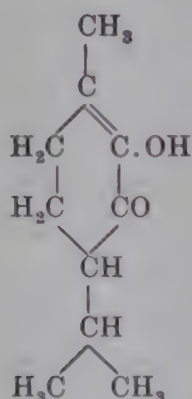


* *Annalen*, 1907, 357, 74.

The constitution of sylvecarvone is uncertain, since, as has been shown on p. 226, sylvestrene is a mixture of the two hydrocarbons represented by (I) and (II) and the nitrosochloride must therefore be either (III) or (IV) or a mixture of the two. *Sylvecarvoxime* must have formula (V) or (VI) and the *ketone* (VII) or (VIII). A distinction between these two formulae could only be arrived at by an investigation of their oxidation products, since both ketones would probably react with aromatic aldehydes (compare piperitone, p. 368).

DIOSPHEENOL (BUCHUCAMPHOR)

(Δ^1 -p-Menthen-2-ol-3-one or
1-Methyl-4-isopropyl- Δ^1 -cyclohexen-2-ol-3-one)



From the leaves (buchu leaves) of various species of *Barosma*, *B. betulina* Bartl., *B. serratifolia* Willd. and *B. crenulata* L., an oil can be separated, which partially crystallises. The properties of the crystalline solid, to which the name buchucamphor or diosphenol has been given, was first investigated by Flückiger,* and it was subsequently studied in more detail by Spica,† Shimoyana‡ and Kondakov *et al.*§ As the outcome of these researches, it was clearly established that diosphenol had the formula $C_{10}H_{16}O_2$ and that it contained a hydroxy group and a carbonyl group. The constitution was elucidated as the result of an elegant investigation by Semmler and McKenzie.||

* *Pharm. J.* 1880, 11, 174, 219.

† *Gazzetta*, 1885, 15, 195.

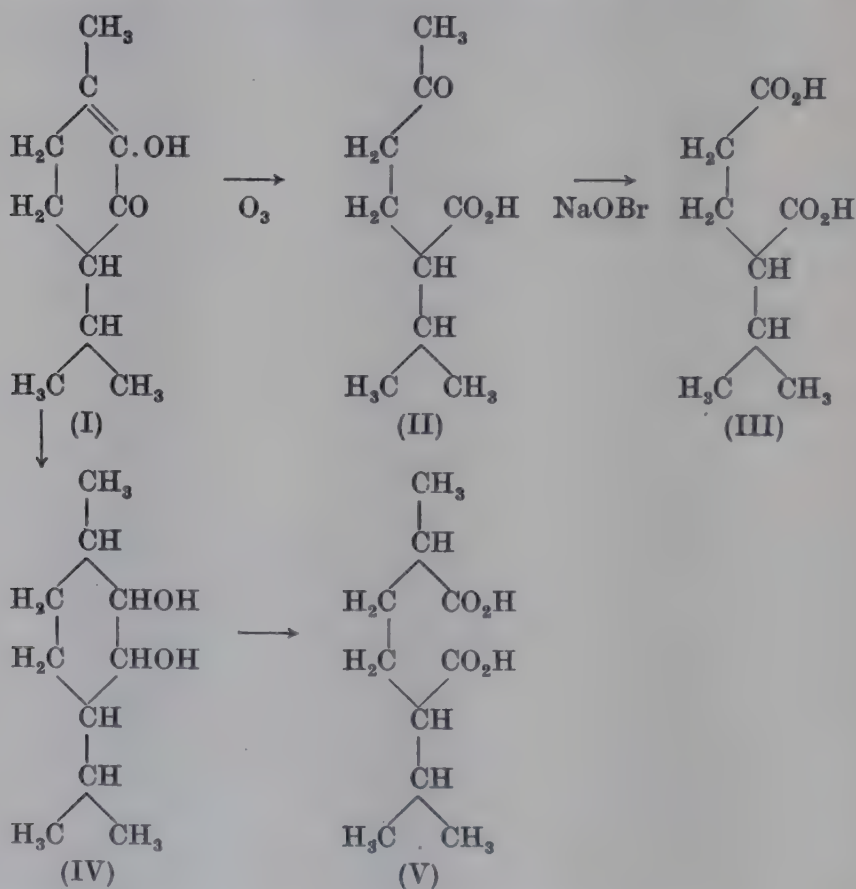
‡ *Arch. Pharm.* 1888, 226, 403.

§ *J. pr. Chem.* 1896 [ii], 54, 433; 1901 [ii], 63, 49.

|| *Ber.* 1906, 39, 1160.

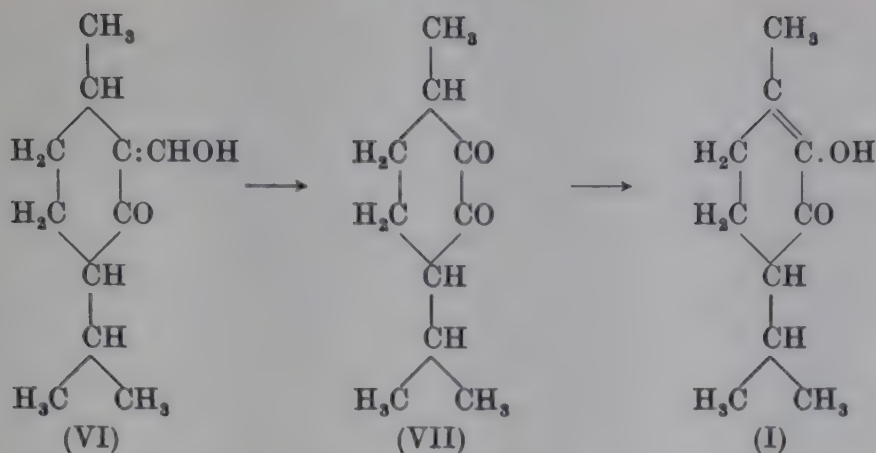
Although diosphenol is attacked with extreme readiness by oxidising agents and reduces both Fehling's and silver solutions, Semmler and McKenzie found that it could be oxidised smoothly with ozone to yield α -isopropyl- γ -acetylbutyric acid (II), m.p. 41° , from which, by treatment with sodium hypobromite, α -isopropylglutaric acid (III) was prepared. The formation of these oxidation products can be explained readily, if diosphenol has the structure represented by (I).

A study of the action of reducing agents on the ketone confirmed this constitution. On reduction with sodium and alcohol, a glycol, $C_{10}H_{20}O_2$, was obtained which must be *p*-menthane-2:3-diol (IV) since, on oxidation with potassium permanganate, it yields α -methyl- α' -isopropyladipic acid (V), m.p. 104° .



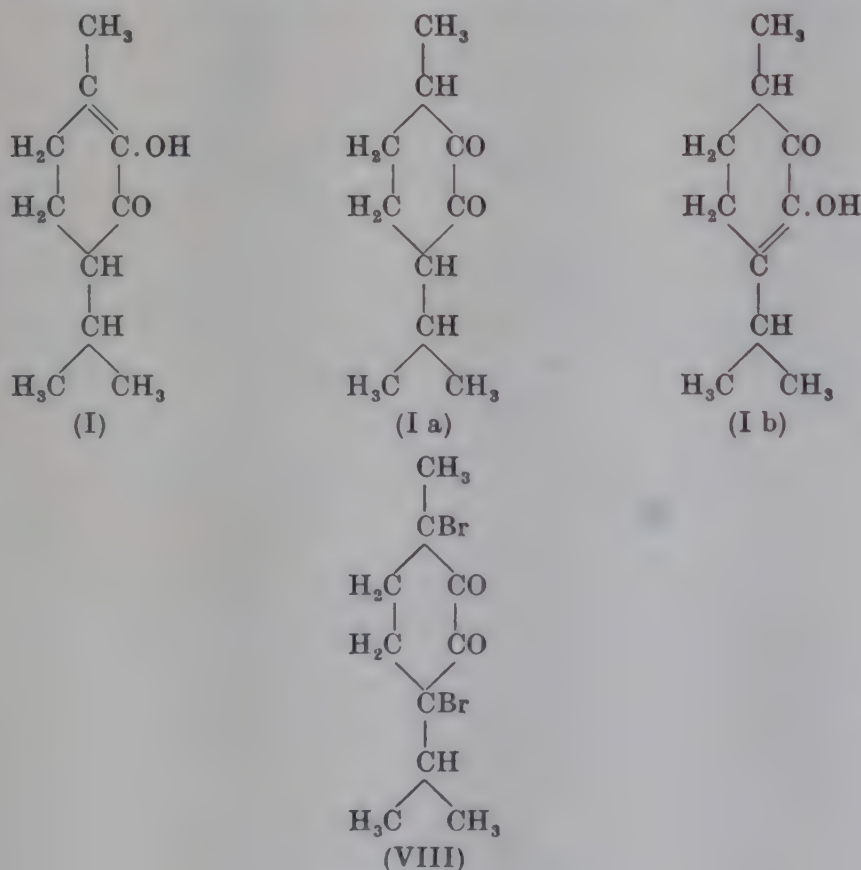
Diosphenol was prepared synthetically by Semmler and McKenzie by the oxidation of *hydroxymethylene menthone* (VI), the diketone (VII) so obtained tautomerising to the hydroxyketone.

Diosphenol has m.p. 83° , b.p. $109\text{--}110^\circ/10\text{ mm.}$; the physical



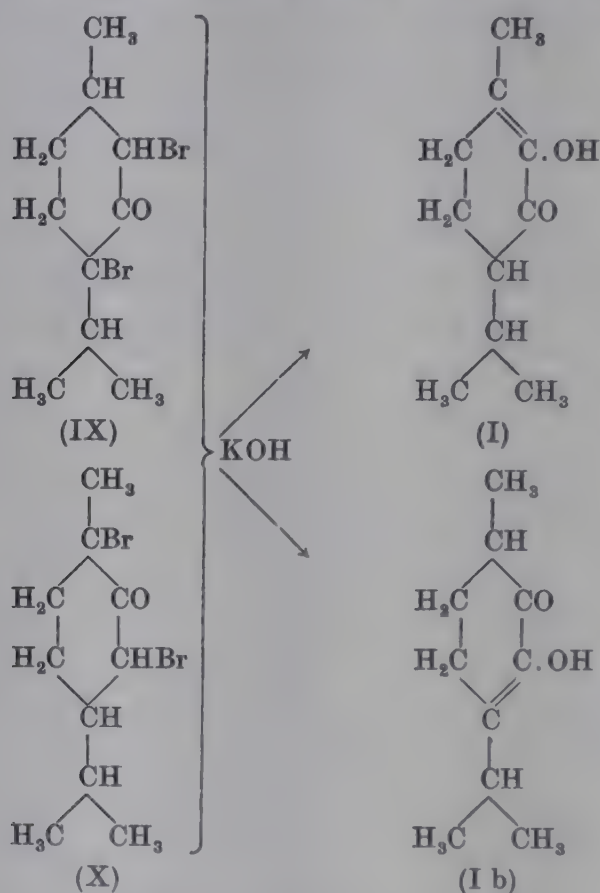
constants of the fused ketone have been determined by Auwers: * $d_4^{99.2^\circ} 0.9542$, $n_D^{99.8^\circ} 1.4607$. It shows a molecular exaltation of $+0.92$, in good agreement with the value which might be anticipated for a hydroxy-ketone containing an ethylenic linkage conjugated with the carbonyl group.

Although the crystalline ketone, m.p. 83° , is undoubtedly correctly represented by formula (I), there is evidence that it can exist also in both its tautomeric forms (I a) and (I b).



* Ber. 1924, 57, 1106.

Evidence for the existence of the diketonic form (I a) was furnished by Wallach,* who, during an investigation of the bromination of the ketone (see below), prepared a yellow *dibromide*, m.p. 44–45°, which in view of its colour and its reactions, must undoubtedly be represented by formula (VIII). Further confirmation of the existence of the diketonic form was obtained† by the preparation of a *dioxime*, m.p. 197°. There is also strong evidence for the existence of the tautomeride (I b). When menthone and carvomenthone dibromides (IX) and (X) are treated with alkali, a mixture of two hydroxy-ketones is formed which



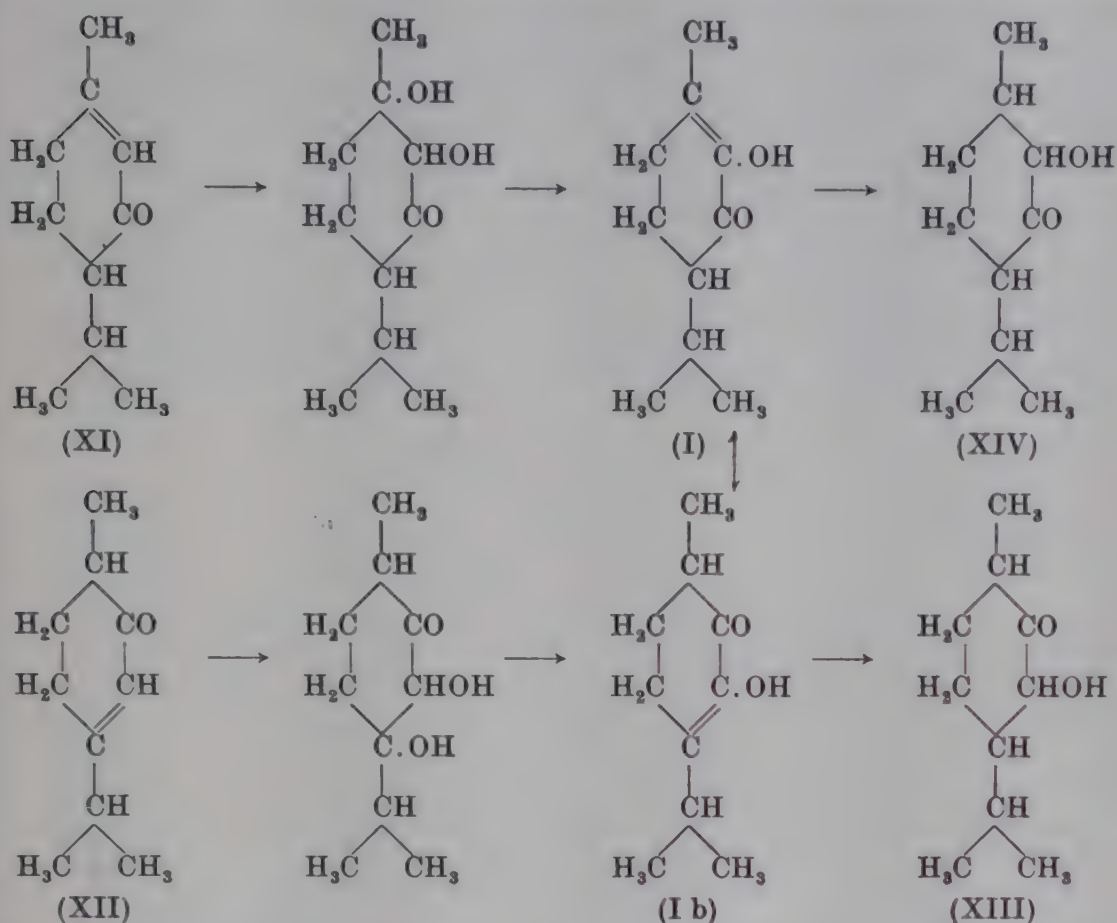
melt at 83° and 36–37° respectively (compare pp. 319, 331). The former of these is identical with diosphenol, whilst the latter, which is unstable and slowly changes into diosphenol, is in all probability the tautomeride (I b). On bromination it behaves like diosphenol.

Further evidence has been provided by the oxidation of *piperitone* (XI) and *carvenone* (XII) with potassium perman-

* *Annalen*, 1919, **418**, 37.

† Wallach, *ibid.* 1924, **437**, 172

ganate.* Whilst piperitone, as would be anticipated, was found to yield diosphenol, carvenone under similar conditions gives an



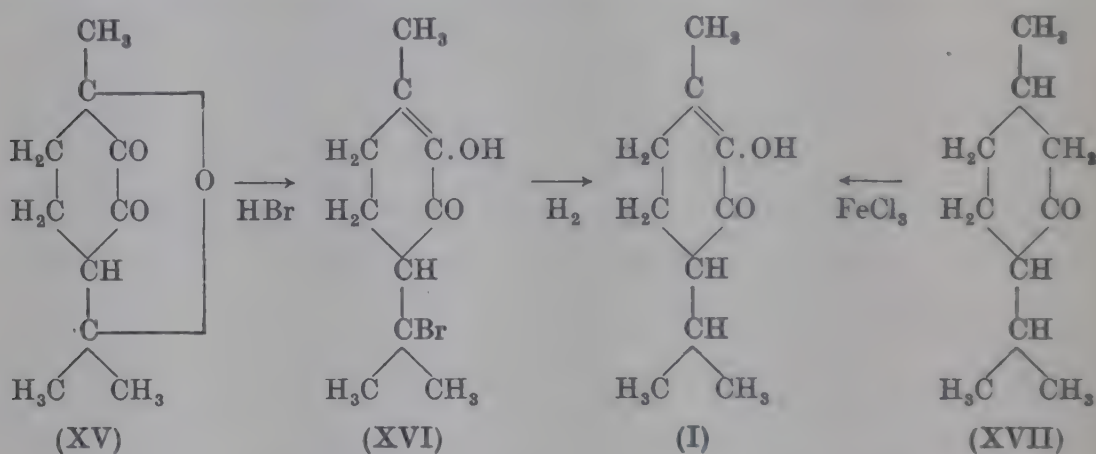
oil, which, on solution in alkali or distillation in steam, passes immediately into diosphenol. This difference is readily accounted for if the reactions proceed in accordance with the scheme set out above. Furthermore, Cusmano[†] has shown that, on catalytic hydrogenation in the presence of platinum black, diosphenol yields a mixture of stereoisomeric 3-hydroxycarvomenthones having the structure (XIII). The two alcohols are oils, which yield *semicarbazones*, m.p. 180–181° and 221°, respectively, and their constitution was established by conversion into carvomenthone by treatment with hydrogen bromide followed by reduction of the bromo-ketone so obtained. It would appear that under these particular conditions of hydrogenation, diosphenol reacts in the form (I b).

* Wallach, *Annalen*, 1924, **437**, 148.

† *Gazzetta*, 1923, **53**, 649.

More recently, Walker and Read,* using a colloidal palladium catalyst, have prepared a *dihydrodiosphenol* which they consider to be 2-hydroxymenthone (XIV) (*semicarbazone*, m.p. 210–211°), since on dehydration it yields piperitone and Δ^4 -p-menthen-3-one. Both of these products have a carbonyl at C₃ and it follows that in this instance diosphenol reacts in the form (I).

In addition to the methods referred to above, diosphenol has been prepared by Cusmano and Massa† from *diketo-cineole* (XV), which, when treated with hydrogen bromide, yields *bromodiosphenol* (XVI), and this, on reduction with zinc dust in alcoholic solution is converted into the hydroxy-ketone.



Finally, Asahina and Mituhori‡ have shown that menthone (XVII) on oxidation with ferric chloride in acetic acid solution, gives diosphenol.

Diosphenol can be identified by its melting-point, 83°, by the intense green coloration which it gives with ferric chloride, and by the preparation of the *phenylurethane*, m.p. 113–114°.

According to Kondakov and Bachtschiev,§ diosphenol on reduction with sodium and alcohol yields a mixture of *dl*-menthol and two isomeric *glycols*, one of which is crystalline, m.p. 92°. Semmler and McKenzie were unable to confirm the formation of menthol, but they obtained a mixture of *glycols*, b.p. 135–137°/10 mm., which partially crystallised. It is probable that these are *cis-trans*-isomerides of the diol (IV), since oxidation with potassium permanganate yields the substituted adipic acid

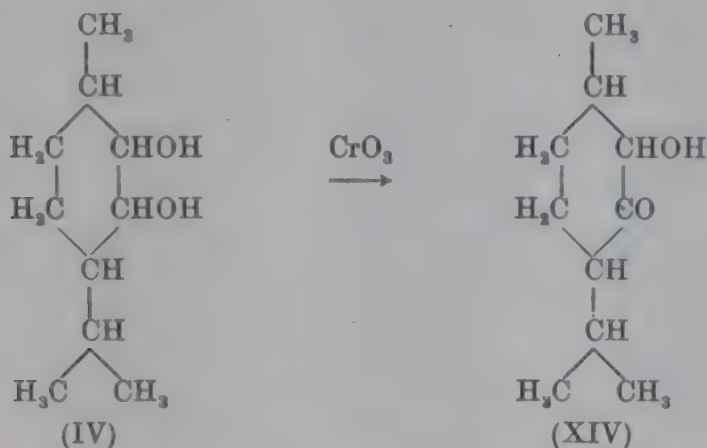
* *J.C.S.* 1934, p. 238.

‡ *J. Pharm. Soc. Japan*, 1922, **482**, 1.

† *Gazzetta*, 1925, **55**, 140.

§ *J. pr. Chem.* 1901 [ii], **63**, 61.

referred to on p. 414. On oxidation with chromic acid a hydroxy-ketone was obtained, the *semicarbazone* of which melted at 200° . This ketone is apparently not identical with either of those prepared by Cusmano by the hydrogenation of diosphenol (p. 417) and it is possibly therefore a stereoisomer of the *hydroxymenthone* (XIV).



By reduction with sodium amalgam, Shimoyama* obtained a ketone, m.p. 159° , which he considered to have the formula, $\text{C}_{10}\text{H}_{18}\text{O}_2$. It is more probable, however, that this substance is a *pinacone*, $\text{C}_{20}\text{H}_{34}\text{O}_4$. Reduction with hydriodic acid and red phosphorus yields *p*-menthane.

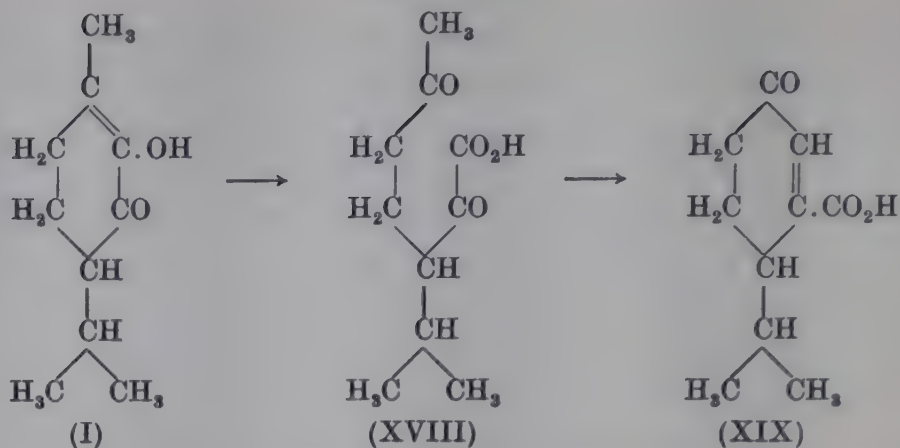
The oxidation of diosphenol with chromic acid results, according to Kondakov and Bachtschiev† in the formation of a crystalline acid, m.p. 45° , which is probably identical with α -isopropyl- γ -acetylbutyric acid (II), m.p. 41° , obtained by Semmler and McKenzie on oxidation with ozone (p. 414). With potassium permanganate, an acid is formed which on keeping or on distillation under diminished pressure loses water with the formation of a ketonic acid, 2-isopropyl- Δ^6 -cyclohexen-5-one carboxylic acid (XIX), m.p. $104\text{--}105^{\circ}$, which results by the loss of water from the primary oxidation product (XVIII).

It is interesting to note that Cusmano‡ obtained this ketonic acid by the oxidation of diosphenol in ethereal solution with either air or oxygen in the presence of platinum black. In this reaction a number of other substances are also formed, but their constitutions have not been determined.

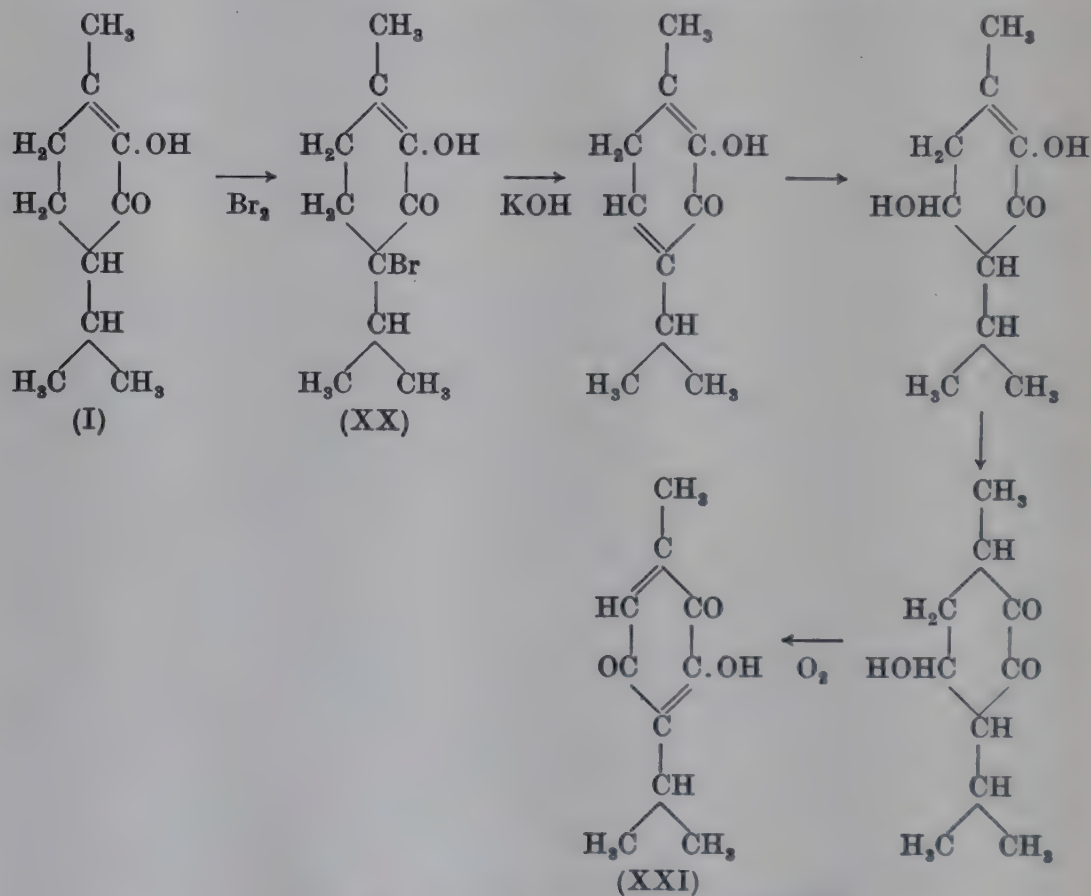
* *Arch. Pharm.* 1888, **26**, 403.

† *J. pr. Chem.* 1901 [ii], **63**, 75.

‡ *Gazzetta*, 1923, **53**, 158.



The bromination of diosphenol, originally investigated by Shimoyama,* was studied later by Cusmano[†] and Wallach.[‡] With one molecule of bromine in acetic acid or chloroform solution, a *bromide*, m.p. 77–78°, is formed, which has the constitution (XX), since on treatment with alkali or pyridine in the presence of air, it yields *hydroxythymoquinone* (XXI) in ac-



* *Arch. Pharm.* 1888, **26**, 403.

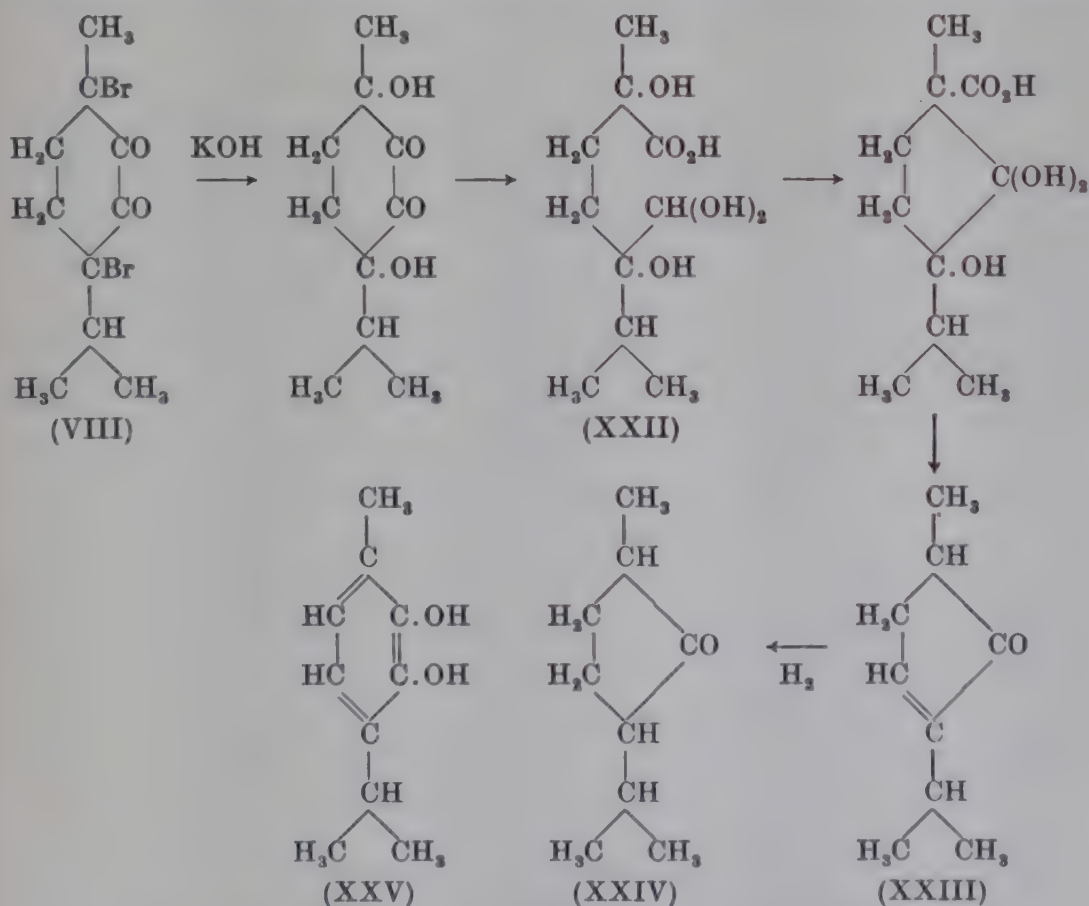
[†] *Atti R. Accad. Lincei*, 1913 [v], **22**, II, 569.

[‡] *Annalen*, 1919, **418**, 37.

cordance with the scheme set out above. According to Wallach, in addition to the above-mentioned bromide, an isomeride, m.p. 100–101°, is also formed in small amount, but its constitution has not been determined.

If the monobromide, m.p. 77°, is treated with a second molecule of bromine or if two molecules of bromine are used in the original reaction, a yellow *dibromide*, m.p. 44–45°, is formed. Reference has been made already to the constitution of this substance (p. 416). On reduction with zinc dust, it is reconverted into the parent ketone, whilst with pyridine it gives hydroxythymoquinone. It reacts in an interesting manner with alkali yielding a hydrated acid, $C_{10}H_{18}O_5$, H_2O (XXII), m.p. 88–89°. This acid, when warmed, loses carbon dioxide and passes into an unsaturated ketone which is probably 5-methyl-2-isopropyl- Δ^3 -cyclopenten-1-one (XXIII), since on catalytic hydrogenation dihydrocamphorone (XXIV) is obtained.

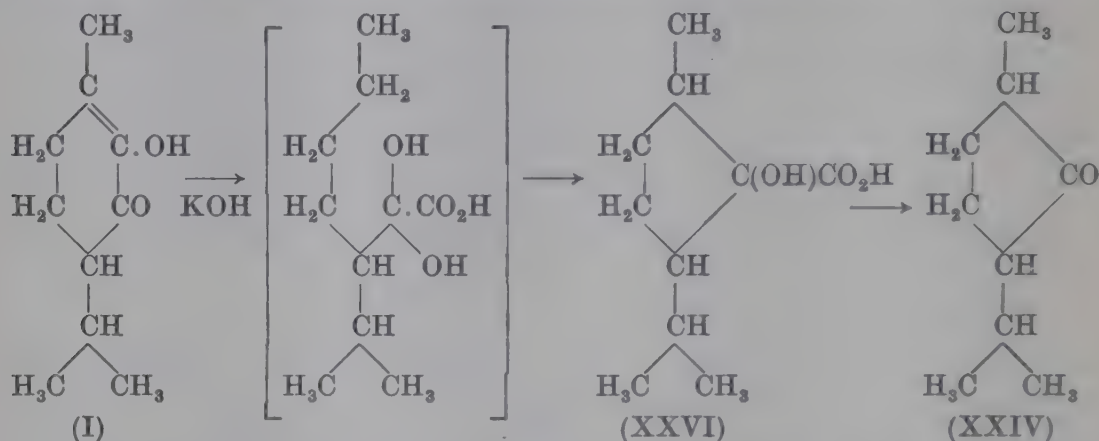
Reference must be made also to the experiments of Cusmano*



* *Atti R. Accad. Lincei*, 1919 [v], 28, II, 30; *Gazzetta*, 1930, 60, 105.

in which he showed that bromodiosphenol, on digestion with acetic anhydride and sodium acetate, yields the *diacetyl* derivative of *methylisopropyl catechol* (XXV). When diosphenol is heated with concentrated hydrochloric acid at 180° under pressure, it gives a mixture of thymol and carvacrol, and when the sodium derivative is heated to 240° (XXV) is formed also.

Diosphenol can also be converted into dihydrocamphorone (XXIV) by the action of alcoholic potassium hydroxide solution at $150\text{--}160^\circ$ under pressure. The primary product of the reaction is a *hydroxy acid* (XXVI), from which, by oxidation with lead peroxide in the presence of sulphuric acid, the ketone is obtained.



The carbonyl group in diosphenol only reacts very sluggishly with reagents, and crystalline derivatives with semicarbazide and phenylhydrazine have not been prepared. The *oxime*, m.p. 125° , was described by Semmler and McKenzie, but it is formed only very slowly. The hydroxyl group, on the other hand, shows very marked phenolic properties and diosphenol is readily soluble in alkalis. A considerable number of derivatives has also been prepared. The *phenylurethane*,* obtained in an impure state by Semmler and McKenzie, melts at $113\text{--}114^\circ$. The *benzoyl* derivative, b.p. $218\text{--}219^\circ/11$ mm., the *acetate*, b.p. $140\text{--}142^\circ/12$ mm., the *methyl ether*, b.p. $240\text{--}242^\circ/750$ mm., and the *ethyl ether*, b.p. $242\text{--}246^\circ/750$ mm., have also been described.†

The absorption spectra of diosphenol and dihydrodiosphenol have been investigated by Lowry and Lishmund.‡

* Asahina and Mituhori (*loc. cit.*); compare Wallach, *Annalen*, 1924, 437, 148.

† Auwers, *Ber.* 1924, 57, 1106; Straneo, *Gazzetta*, 1940, 70, 27.

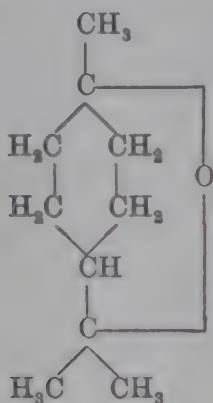
‡ *J.C.S.* 1935, p. 1313; compare Gillam, Lynas-Gray, Penfold and Simonsen, *ibid.* 1941, p. 62.

CHAPTER V

OXIDES

1:8-CINEOLE

(Anhydride of *p*-Menthane-1:8-diol or
Anhydride of 1-Methyl-4-isopropylcyclohexane-1:8-diol)



1:8-Cineole, C₁₀H₁₈O, is one of the most widely distributed constituents of essential oils and it possesses the additional interest of forming the starting-point (in 1884) of Wallach's classical researches in terpene chemistry. For a detailed list of the oils in which cineole has been found reference should be made elsewhere,* and mention need only be made here to its occurrence in wormseed oil, *Oleum Cinae*, from *Artemisia maritima* L., oil of cajuput from *Melaleuca minor*, and in various *Eucalyptus* oils.

The study of the chemistry of cineole, which is also known as *eucalyptol* and *cajuputol*, dates back to about 1840. It was not, however, until much later (1885), that the identity of the oxygenated constituent, b.p. about 173°, of wormseed, cajuput and eucalyptus oils was recognised. As a result, there were three simultaneous and converging series of investigations in progress.

The investigation of wormseed oil was first undertaken by Trommsdorf,[†] whilst Voelkel* in 1841 suggested that the main constituent of this oil was a substance of the formula C₉H₁₅O,

* Gildemeister and Hoffmann, *Die Ätherischen Öle*, 1923, Vol. I, p. 661.

[†] Trommsdorf *Neues J.* 3, 12.

* *Annalen*, 1841, 38, 110; 1854, 89, 358.

which, on treatment with phosphorus pentoxide, was converted into a hydrocarbon, "cynene", b.p. 173–175°. Kraut* found that cineole always occurred mixed with a hydrocarbon, from which it could not be separated, but he succeeded in assigning the correct formula, $C_{10}H_{18}O$, and later, in collaboration with Wahlforss,† he showed that "cynene" had the formula $C_{10}H_{16}$. These authors were also the first to prepare an additive compound of cineole, namely that formed with iodine.

Cineole was not obtained pure until 1884, when Hell and Stürcke‡ prepared the oxide, in what may be regarded as a practically pure state, by removing the admixed hydrocarbon by oxidation with a dilute solution of potassium permanganate. These also found that "cynene" gave *p*-cymene sulphonic acid on treatment with sulphuric acid. The action of hydrogen chloride on cineole was studied by Hell and Ritter,§ who showed that an additive compound was first formed, from which cineole could be regenerated. If, however, the additive compound was warmed, it passed into "cynene" dihydrochloride. From these experiments Hell and Ritter reached the conclusion that cineole was an oxide.

The investigation of oil of cajuput followed a somewhat similar course. In 1833 Blanchet|| showed that this oil consisted mainly of a substance, b.p. 175°, which had the composition $C_{10}H_{18}O$. This was confirmed by Schmidt,¶ who prepared from cajuputol, by the action of sulphuric acid, a crystalline substance, $C_{10}H_{16}$, $3H_2O$, which was undoubtedly terpin hydrate. Schmidt also observed that cajuputol gave with hydrogen chloride an additive compound, whilst with aqueous hydrochloric acid dipentene dihydrochloride was formed.

In 1884, practically simultaneously with the investigations of Hell and his collaborators, Wallach and Brass** described the purification of cajuputol by decomposition of the additive compound, $(C_{10}H_{18}O)_2HCl$, which it formed with hydrogen chloride. They observed the formation of a dibromide, $C_{10}H_{18}O$, Br_2 , which on keeping passed gradually into dipentene tetrabromide, and suggested that cineole and cajuputol were identical.

* *Arch. Pharm.* 1850, 111, 104.

† *Annalen*, 1863, 128, 293.

‡ *Ibid.* 1884, 17, 1975.

§ *J. pr. Chem.* 1861, 82, 189.

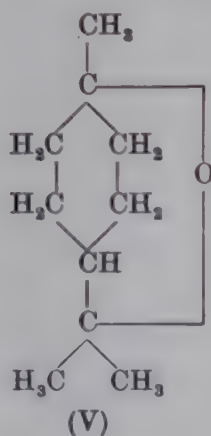
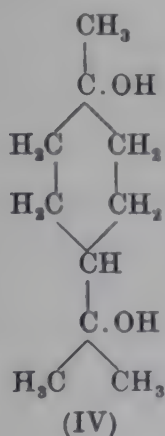
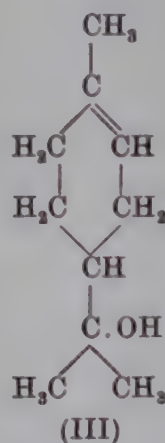
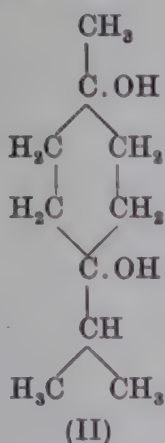
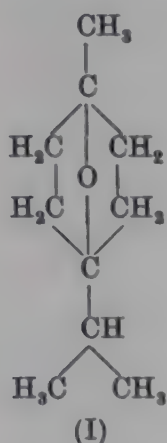
¶ *Ber.* 1884, 17, 1970.

|| *Annalen*, 1833, 7, 161.

** *Annalen*, 1884, 225, 291.

Eucalyptol, from *Eucalyptus globulus*, was first studied by Cloez* and later by Jahns,† who showed it to be identical with cineole.

Although Hell and Ritter had reached the conclusion that cineole was an oxide, they did not suggest any constitutional formula, and it was not until the following year that Richter‡ proposed (I), a formula which received general acceptance, since it explained the reactions of the oxide so far as they were known. Thus, for example, it accounted for the formation of cineole by the dehydration of terpin, for the conversion of the oxide into dipentene hydrochloride by the action of hydrochloric acid, and into the hydrocarbons, dipentene, terpinene and terpinolene by the action of dehydrating agents.§



At the time during which these experiments were carried out, terpin was erroneously considered to be represented by formula

* *Compt. rend.* 1870, **70**, 687.

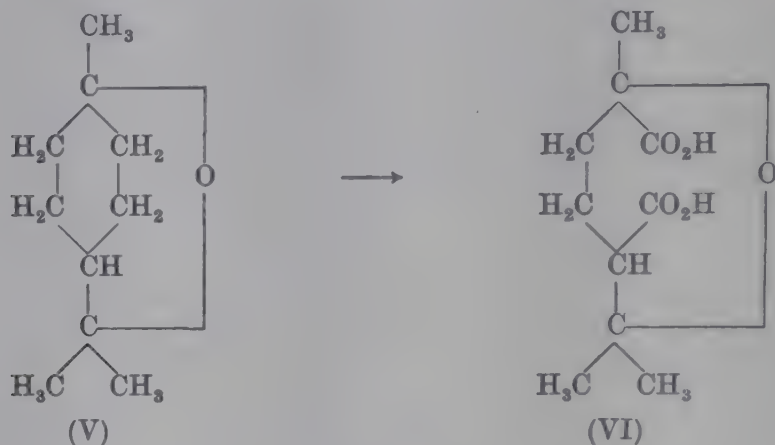
† *Ber.* 1884, **17**, 2941; *Arch. Pharm.* 1885, **223**, 52.

‡ *Dissertation*, Stuttgart, 1885.

§ *Inter al.*, Wallach, *Annalen*, 1885, **230**, 268; 1887, **239**, 23.

(II), but in 1895 (see p. 259) it was definitely proved that α -terpineol had formula (III); it was necessary, therefore, to modify the formula for terpin and cineole to (IV) and (V).

In the meantime the oxidic formula for cineole had received further support from the investigations of Wallach and his collaborators,* who had shown that on oxidation with potassium permanganate, an oxidic acid, *cineolic acid* (VI), $C_{10}H_{16}O_5$, m.p. 204–206°, was formed.



This acid undergoes a number of interesting reactions, which, together with the proof of its constitution, are discussed on p. 427.

The relationship of cineole to α -terpineol and terpin and its oxidation to cineolic acid leave no doubt that its constitution is correctly represented by (V). In view of W. H. Perkin jun.'s synthesis of terpin (see p. 302), cineole may also be regarded as having been prepared by a rational synthesis.

For the characterisation of cineole, a number of methods are available all of which depend upon the great facility with which it forms additive compounds. These methods have been studied with care in view of its use in pharmacy and the technical importance of the accurate quantitative estimation of the oxide. Cineole may be separated by the preparation of its crystalline compounds with phosphoric acid, the halogen acids, or substituted phenols. For full details of the precautions necessary in the preparation of these derivatives, books on essential oil analysis should be consulted.

* *Annalen*, 1888, **246**, 268; 1890, **258**, 319; 1892, **271**, 20.

1:8-Cineole is a colourless viscid oil possessing a characteristic camphoraceous odour. When cooled to a low temperature, it can be obtained crystalline and then melts at 1° , b.p. $174.4^{\circ}/760$ mm.; $63^{\circ}/15$ mm., $d^{15^{\circ}} 0.930$, $n_D^{20^{\circ}} 1.4575$.*

Cineole is a substance of marked stability and it can be distilled unchanged over sodium. It is not attacked by the ordinary reducing agents, nor can it be reduced by the Sabatier-Senderens method, but when distilled in a current of hydrogen over nickel at $350-360^{\circ}$ it is dehydrogenated yielding *p*-cymene.†

It was mentioned above that on oxidation with potassium permanganate, cineole gave a dibasic acid, cineolic acid (VI), and in view of the important bearing of this acid on the constitution of cineole and its interesting reactions it is necessary to consider it in some detail. It was observed by Wallach‡ that when the acid was digested with acetic anhydride or distilled under diminished pressure it was converted into an *anhydride* (VII), m.p. $77-78^{\circ}$. This anhydride, when distilled at the ordinary pressure, yields *methyl heptenone* (VIII).

We owe to Rupe and his collaborators§ the results of a very detailed study of the further reactions of cineolic acid. Rupe and Ronus found that, when cineolic acid was heated with water under pressure at 160° , addition of water and loss of carbon dioxide took place with formation of the dihydroxy acid, *cinogenic acid* (IX), m.p. $104.5-105^{\circ}$. This acid, when heated to 150° , lost water yielding the oxido-monobasic acid, α -*cinenic acid* (X), m.p. $83-84^{\circ}$ (*p*-*bromophenacyl ester*, m.p. $98-99^{\circ}$). This acid can also be prepared directly from cineolic acid by heating under pressure with dilute sulphuric acid.

The constitution of α -cinenic acid was proved by its synthesis by Rupe and Schlochoff.¶ Starting with methyl heptenone (VIII), they hydrated this to the ketonic alcohol (XI) and from this the *hydroxynitrile* (XII) was prepared, which immediately lost water with formation of the *nitrile* of cinenic acid (XIII). This nitrile, on hydrolysis with alkali, gave α -cinenic acid

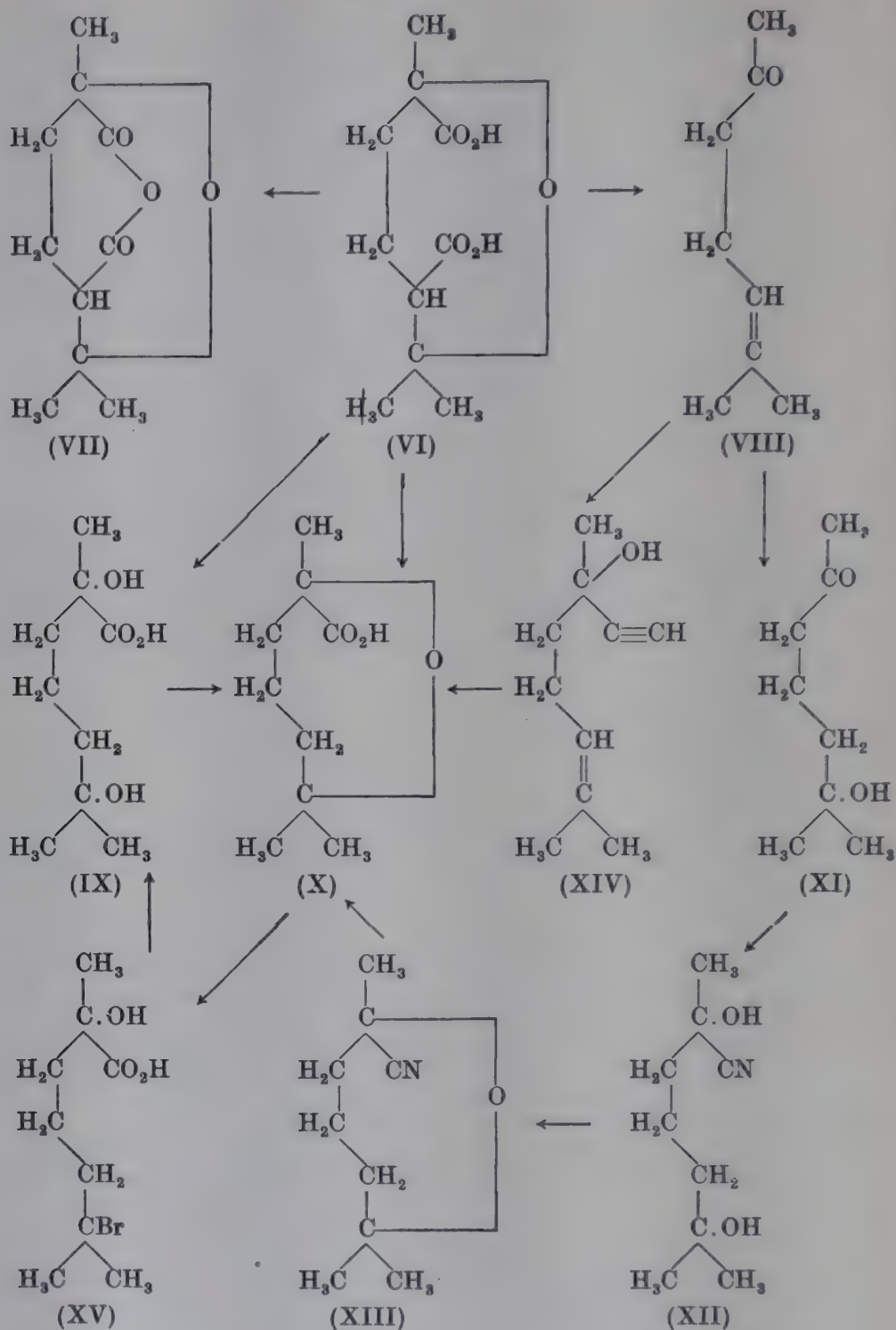
* Berry and Swanson, *Perfum. essent. Oil Rec.* 1932, **23**, 371.

† Sabatier and Gaudion, *Compt. rend.* 1919, **168**, 671.

‡ *Annalen*, 1888, **246**, 268; 1890, **258**, 319; 1892, **271**, 20.

§ *Ber.* 1900, **33**, 1129, 3541; 1901, **34**, 2196, 2204; 1906, **39**, 4076, 4083; 1908, **41**, 3955; *J. pr. Chem.* 1917 [ii], **96**, 59.

¶ *Ber.* 1905, **38**, 1503.

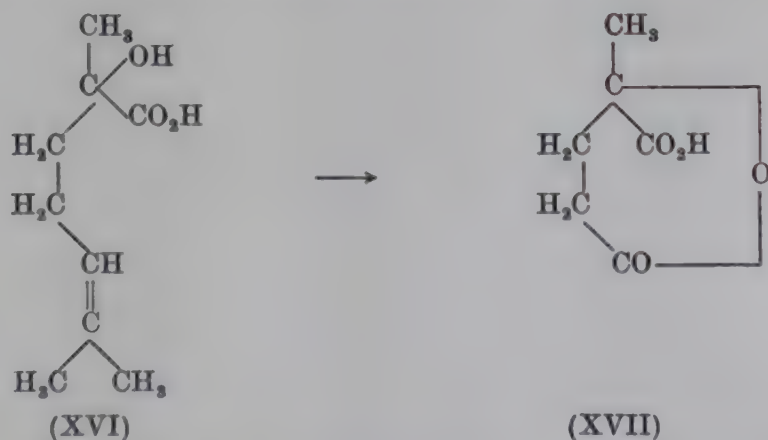


identical in all respects with the acid obtained by the removal of carbon dioxide from cineolic acid. A simpler synthesis* involves the condensation of methyl heptenone (VIII) with acetylene, followed by oxidation of the acetylene carbinol (XIV).

* Rupe and Lang, *Helv. Chim. Acta*, 1929, 12, 1137.

When α -cinenic acid is treated with hydrogen bromide the oxidic ring undergoes fission with formation of ϵ -bromo- α -hydroxy- $\alpha\epsilon$ -dimethylheptoic acid (XV), which on treatment with alkali is converted into cinogenic acid (IX).

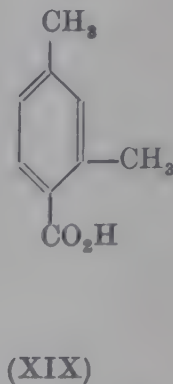
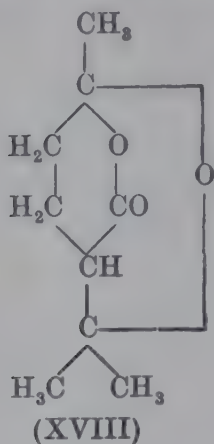
It is always observed in the preparation of α -cinenic acid that it is mixed with an isomeric liquid acid, b.p. $124.5\text{--}125^\circ/12\text{ mm.}$ (*p*-bromophenacyl ester, m.p. 66°). This acid, which is known as β -cinenic acid, has been very carefully studied by Rupe and Altenburg and by Rupe and Blechschmidt. The two acids can be most readily separated by taking advantage of the fact that when a mixture of the two is esterified with methyl alcohol in the presence of hydrogen chloride, the α -acid gives the *methyl* ester of the *chloro*-acid corresponding to (XV), whilst the β -acid gives the normal ester. These two esters are readily separable by distillation and on hydrolysis the β -ester gives the pure liquid β -acid. The α -acid, when heated under pressure with dilute sulphuric acid, is completely converted into its β -isomeride, and for many years the latter was thought to be closely related structurally to the α -acid, particularly in view of the fact that the same bromo-acid (XV) is formed from both by the action of hydrogen bromide. The later investigations of Rupe and Hirschmann* have shown, however, that β -cinenic acid is 1:5-dimethyl- Δ^4 -hexen-1-ol-1-carboxylic acid (XVI), since on ozonolysis it yields α -methylparaconic acid (XVII).



Treated with concentrated sulphuric acid in the cold, cineolic acid yields the *lactone* (XVIII), carbon monoxide being elimi-

* *Helv. Chim. Acta*, 1933, 16, 505; 1934, 17, 98.

nated, and this lactone, when warmed with the same reagent, passes into 1:3-dimethylbenzene-4-carboxylic acid (XIX).



Finally, reference may be made to the fact that Rupe and Ronus resolved cineolic acid by means of its strychnine salt into its optically active components, which melt at 138–139°.

The formation of liquid chloro-compounds by the action of chlorine on cineole has been reported by Gandini* and by Delaby and Billuart.† Cineole reacts with bromine in ligroin solution to yield a red crystalline compound which, according to Wallach and Brass,‡ has the composition $C_{10}H_{18}OBr_2$. This compound is unstable and if kept for some time in a sealed tube passes into dipentene tetrabromide. According to Wallach,§ it is possible also to prepare a bromide of the composition $(C_{10}H_{18}O)_2Br_2$.

With hydrogen chloride in ligroin solution, an additive compound, $(C_{10}H_{18}O)_2HCl$, is formed,|| whilst that obtained with hydrogen bromide¶ has the composition $C_{10}H_{18}OHBr$. The latter compound is more readily formed and melts at 56–57°; it may be used for the characterisation of cineole. Both these halogen derivatives pass on keeping into the corresponding dipentene dihydrohalides. In 1892 Baeyer** made the interesting observation that when an acetic acid solution of cineole was treated with hydrogen chloride, in addition to the ordinary dipentene dihydrochloride, m.p. 50°, a lower melting form, m.p. about 25°, was

* *Gazzetta*, 1933, **63**, 151; 1934, **64**, 118, 302; 1939, **69**, 177.

† *Bull. Soc. chim.* 1943, **10**, 567.

‡ *Annalen*, 1884, **225**, 303.

§ Wallach and Brass, *ibid.* 1884, **225**, 291.

¶ Wallach and Gildemeister, *ibid.* 1888, **246**, 280.

‡ *Ibid.* 1885, **230**, 228.

** *Ber.* 1893, **26**, 2863.

obtained. This latter was regarded by Baeyer as *cis-dipentene dihydrochloride*, the *trans*-form melting at 50° . With hydrogen bromide, the *cis-dihydrobromide*, m.p. 39° , was obtained, the *trans*-form melting at 64° . The formation of these derivatives of dipentene from cineole cannot be taken as evidence of any particular stereochemical configuration for cineole, since it is now well recognised that the scission of an oxide ring is frequently accompanied by a Walden inversion.

The iodine derivatives of cineole, studied originally by Wallach and Brass, have been reinvestigated by Fromm and Fluck.* When cineole is treated with iodine-free hydriodic acid dipentene dihydriodide is formed, but in the presence of free iodine, a dark green additive compound is obtained, from which cineole can be regenerated by treatment with alkali. This substance would appear to be identical with the iodo-derivative described by Wallach and Brass, which was given the formula $(C_{10}H_{18}O)_2I_2$. When cineole is shaken with an acidified solution of potassium iodide, a substance of the composition $C_{10}H_{18}OI_2$, $C_{10}H_{18}O \cdot HI$, is formed, and this can be used for the quantitative estimation of the oxide.

Baeyer and Villiger† prepared from cineole a number of co-ordinated compounds, for a description of which reference should be made to the original memoir. Attention need only be directed here to the compound formed with resorcinol, $(C_{10}H_{18}O)_2$, $C_6H_6O_2$, m.p. $80-85^{\circ}$, and that with *o*-cresol, $C_{10}H_{18}O$, C_7H_8O , m.p. 55.5° . The use of the latter for quantitative estimation of cineole has been advocated by Cocking.‡

The crystalline additive compound formed with phosphoric acid has the composition $C_{10}H_{18}O$, H_3PO_4 , m.p. 80° , and a similar compound is formed with arsenic acid. Of interest also is the iodol derivative, m.p. 112° , which has the formula $C_{10}H_{18}O$, C_4HI_4N .

The action of methyl magnesium iodide on cineole was first examined by Grignard,§ who found that it gave an additive compound, which decomposed on warming. The reaction was

* *Annalen*, 1914, **405**, 175.

† *Ber.* 1901, **34**, 2689; compare Bellucci and Grassi, *Gazzetta*, 1913, **43**, II, 712; Dodge, *J. Amer. Pharm. Assoc.* 1933, **22**, 20.

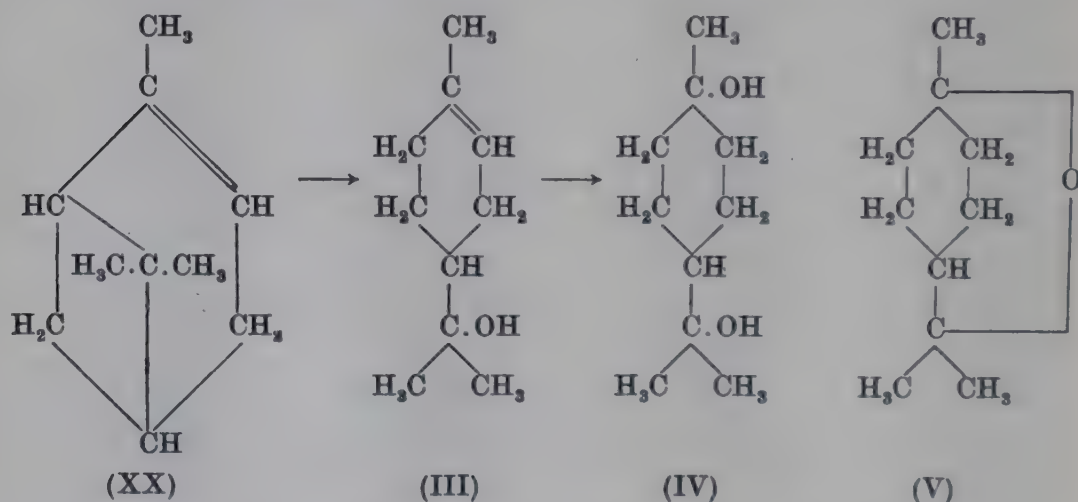
‡ *Pharm. J.* 1920, **105**, 81.

§ *Bull. Soc. chim.* 1903 [iii], **29**, 944.

investigated also by van Duin,* who showed that decomposition of the compound commences at 160° , with evolution of gas and distillation of a liquid. The oil consists of a mixture of hydrocarbons, $C_{10}H_{16}$, b.p. $170\text{--}178^{\circ}/759\text{ mm.}$, but the nature of the constituents was not determined.

When cineole is digested with acetic anhydride in the presence of various catalysts, a mixture of about equal quantities of terpin diacetate and α -terpineol acetate is obtained. With acetic anhydride containing a considerable proportion of sulphuric acid, simultaneous dehydration and condensation to a diterpene, *dicynene*, $C_{20}H_{32}$, is observed.†

Although we have no direct evidence as to the mechanism of the formation of cineole in plants, its very frequent occurrence in oils containing α -terpinene can be accounted for readily, if it be assumed to be formed from either α -pinene (XX) or α -terpineol (III), when terpin (IV) may be regarded as an intermediate product. It will be noticed that this process is analogous to that suggested on p. 435 to account for the formation of 1:4-cineole.

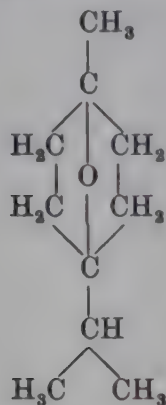


* *Proc. K. Akad. Wetensch. Amsterdam*, 1917, 25, 1366.

† Knoevenagel, *Annalen*, 1913, 402, 138.

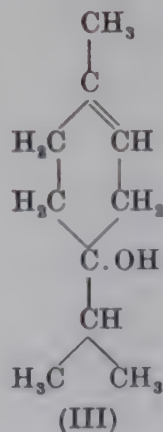
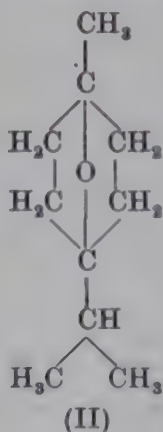
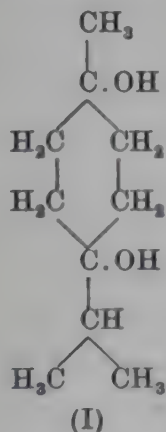
1:4-CINEOLE

(Anhydride of *p*-Menthane-1:4-diol or
Anhydride of 1-Methyl-4-isopropylcyclohexane-1:4-diol)



1:4-Cineole, $C_{10}H_{18}O$, was first described by Wallach* and was subsequently more fully investigated by the same author,[†] but its occurrence in nature has only been established comparatively recently (see below).

It was observed by Wallach that when *trans*-terpinene-terpin (I) (see p. 304) was mixed with a concentrated solution of oxalic acid and steam passed through the solution, a volatile oil was obtained which boiled over a wide range (175–206°). This oil was found to be a mixture of 1:4-cineole (II) and an alcohol, 1-methyl-4-isopropyl- Δ^1 -cyclohexen-4-ol (III).



The unsaturated alcohol was readily removed by treatment of the mixture with potassium permanganate, the oxide being only slowly attacked by this reagent.

* *Annalen*, 1907, 356, 204.

† *Ibid.* 1912, 392, 62.

Some years later, Wallach* obtained a new *terpinene-terpin*, m.p. 116–117°, from ascaridole (see p. 447) and found that this on dehydration with oxalic acid also gave 1:4-cineole. Austerweil† and Marot‡ have shown that 1:4-cineole is present in the low-boiling fractions of the oil obtained in the technical preparation of α -terpineol, and according to Mosher§ it is present with 1:8-cineole in the dehydration products of terpin.

The constitution of the oxide follows directly from its method of preparation and also from the fact that on treatment with hydrogen chloride it yields terpinene dihydrochloride.

1:4-Cineole, b.p. 172°, d_{20}^{18} 0.9010, n_D^{18} 1.4479, has a camphoraceous odour and differs very considerably in its properties from the 1:8-isomeride. In ligroin, it gives no precipitate with hydrogen bromide, but it is slowly converted into terpinene dihydrobromide, m.p. 58–59°; on treatment with bromine in the same solvent, it yields a bright red crystalline precipitate, the nature of which has not been determined. It is only very slowly oxidised by potassium permanganate even in a hot solution and the main product of the reaction is a sparingly soluble acid, m.p. 157°, the constitution of which is not known.¶

From the above summary of the properties of 1:4-cineole, it will be obvious that this oxide cannot be readily characterised and this probably accounts for the fact that its occurrence in nature has only comparatively recently been established. In 1928 Rao, Shintre and Simonsen¶ separated from the essential oil from the fruits of *Piper Cubeba* Linn., grown in Mysore, a fraction (b.p. 109–112°/100 mm.) having a strong camphoraceous odour and which analysis showed to have the composition of an oxide, $C_{10}H_{18}O$. This oil gave with hydrogen chloride terpinene dihydrochloride and, on oxidation with potassium permanganate, a sparingly soluble acid, m.p. 157°, together with a small quantity of caronic acid. There would appear to be no doubt, therefore, that the above-mentioned fraction of the oil from *P. Cubeba* consisted of 1:4-cineole mixed with a little d - Δ^4 -

* *Annalen*, 1907, 356, 204.

† *Bull. Soc. chim.* 1929 [iv], 45, 862.

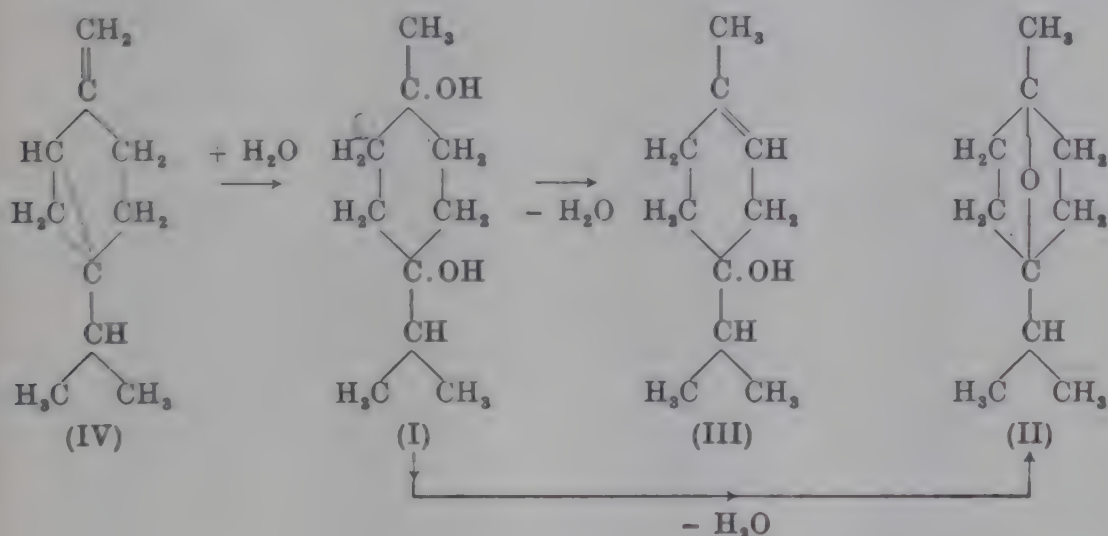
‡ *Bull. Inst. Pin*, 1933 [2], p. 3861.

§ Stevens and Greenwood, *J. Amer. C.S.* 1943, 65, 2154, footnote 11.

¶ Marot (*loc. cit.*) has obtained an acid, m.p. 203–204°, from this reaction; it is possible, however, that this was cineolic acid, derived from 1:8-cineole which might well have been present in his material.

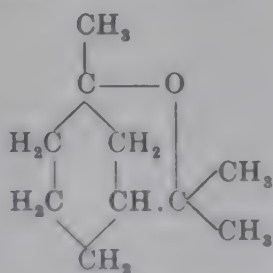
¶ *J.S.C.I.* 1928, 47, 92.

carene.* The occurrence of 1:4-cineole in this oil is of phytochemical interest since it was shown to contain, in addition to the oxide, *dl*-sabinene (IV) and *d*-1-methyl-4-isopropyl- Δ^1 -cyclohexen-4-ol (III). The close relationship of these substances will be readily seen from a consideration of their formulae, their inter-conversion merely requiring the addition or subtraction of water with the intermediate formation of 1:4-terpin (terpinene-terpin) (I).



m-CINEOLE

(Anhydride of *m*-Menthane-1:8-diol or
Anhydride of 1-Methyl-3-isopropylcyclohexane-1:8-diol)

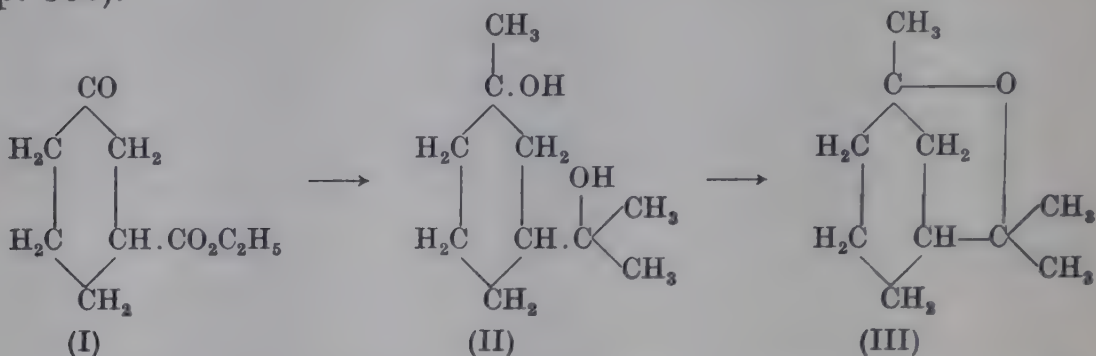


m-Cineole (III) was prepared by Perkin and Tattersall,[†] who obtained it as one of the products of the action of methyl magnesium iodide on *ethyl* cyclohexanone-3-carboxylate (I). It is probably formed by the dehydrating action of the Grignard

* For proof of the presence of this hydrocarbon the original communication should be consulted.

[†] *J.C.S.* 1907, 91, 503.

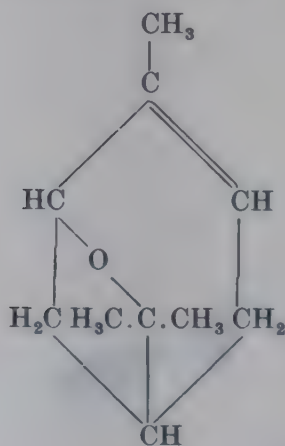
reagent on *cis-m-menthane-1:8-diol* (II), the *trans*-modification of which was actually separated from the reaction products (see p. 306).



m-Cineole is a colourless oil, readily volatile in steam and having a most pungent odour of camphor. It boils at 177–178°/765 mm. According to Perkin and Tattersall it appears to form salts similar to those which are so characteristic of 1:8-cineole, but these have not been investigated. In a solution of hydrogen bromide in acetic acid, *m*-cineole dissolves at once with evolution of heat and in a short time an oil is deposited. From this oil a small quantity of *trans*-carvestrene dihydrobromide, m.p. 48–49°, can be separated, but the greater part does not crystallise and probably consists of the *cis*-modification, the reaction proceeding in a manner similar to that observed in the case of 1:8-cineole (compare p. 430).

PINOL

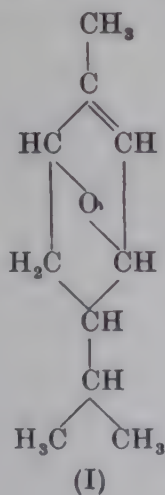
(Anhydride of Δ^1 -*p*-Menthene-6:8-diol or
Anhydride of 1-Methyl-4-isopropyl- Δ^1 -cyclohexene-6:8-diol)



The oxide, *pinol*, which up to the present does not appear to have been found in nature, was probably first prepared by Sobrero* in 1851 by the action of dilute mineral acids on *sobrerol*, but the isolation of the oxide was due to Wallach and Otto,† and we are indebted mainly to the prolonged researches of Wallach and his collaborators for our knowledge of the constitution and properties of this oxide.

Wallach and Otto subjected the by-products from the preparation of pinene nitrosochloride to distillation in steam and obtained a volatile oil, from which a fraction, b.p. 183–184°, was separated which was nearly pure *pinol*. This new substance, $C_{10}H_{16}O$, contained one ethylenic linkage, since on treatment with bromine it gave a crystalline dibromide, *pinol dibromide*, m.p. 94°; it could be converted readily into *p*-cymene and on oxidation gave terebic acid. Wallach tentatively suggested, therefore, that it might be represented by (I).

Continuing his study of the reactions of *pinol*, Wallach‡ in the following year observed that the alcohol *sobrerol* (*pinol hydrate*) gave on treatment with dilute mineral acids *pinol*, a reaction investigated simultaneously by Armstrong.§ In the same communication Wallach described the conversion of *pinol* into *pinol hydrate* with the intermediate formation of *pinol*



hydrobromide. An important advance in the chemistry of *pinol* was made three years later,|| when it was found that the oxide

* *Compt. rend.* 1851, 33, 67.

† *Ibid.* 1890, 259, 315.

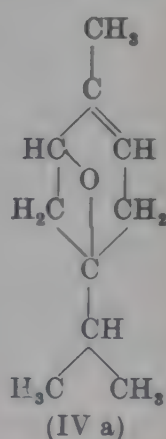
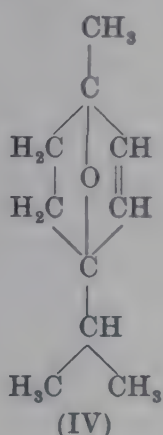
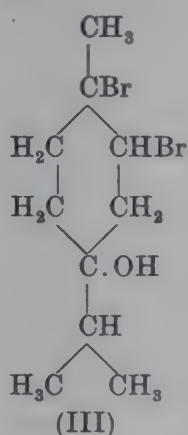
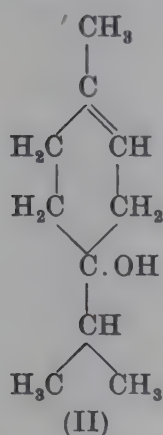
|| Wallach, *Annalen*, 1893, 277, 133.

† *Annalen*, 1889, 253, 249.

§ *J.C.S.* 1891, 59, 314.

could be prepared by the action of sodium ethoxide on α -terpineol dibromide. Wagner* had previously, on purely theoretical grounds, suggested various formulae for pinol, pinol hydrate and related bodies, and in 1894† he published the results of an investigation of the oxidation of pinol and pinol hydrate with potassium permanganate, when *pinol glycol*, *terpenylic* and *terebic acids* were formed. It may be mentioned that Wallach had shown already that the *acetyl* derivative of *pinol glycol*, $C_{10}H_{16}O(OH)_2$, m.p. 125° , could be prepared by the action of silver or sodium acetate on pinol dibromide.

The preparation of pinol from α -terpineol dibromide reduced very considerably the number of possible formulae for pinol. At the time of these experiments α -terpineol was erroneously regarded as having formula (II) and terpineol dibromide (III),



which allowed of pinol being represented by either (IV) or (IV a). The latter formula was preferred since pinol on oxidation did not give cineolic acid, which would have been anticipated if (IV) was correct.‡

The acceptance of Wagner's formulae (V) and (VI) for α -terpineol and α -terpineol dibromide respectively (see p. 259) rendered necessary a revision of the formula of pinol, which it now became obvious must be represented by (VII).§

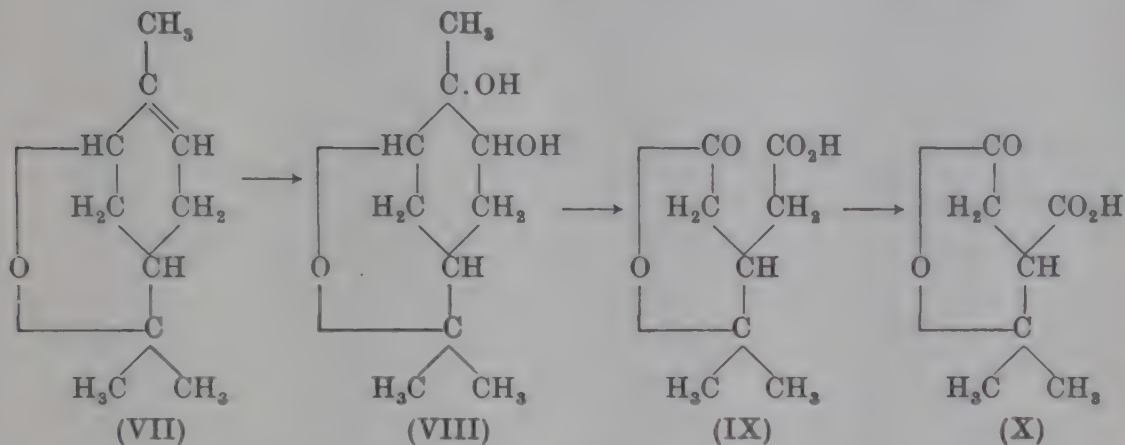
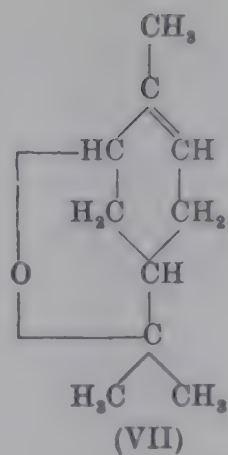
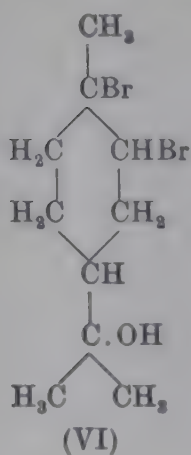
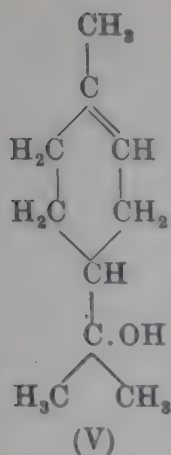
This constitutional formula for pinol accounts satisfactorily for its oxidation to pinol glycol (VIII), terpenylic acid (IX) and terebic acid (X), and, as will be seen from the sequel, it is in full accord with the interesting properties of this oxide.

* Ber. 1891, 24, 2189.

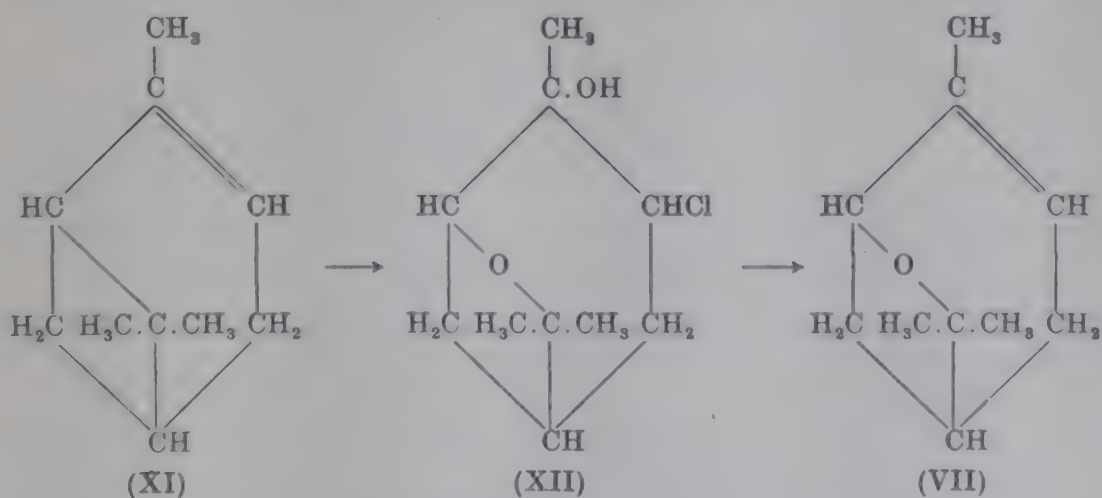
† Ibid. 1894, 27, 1644.

‡ Cineole was at the time considered to be the 1:4-oxide (see p. 425).

§ Wallach, Ber. 1895, 28, 2709; Annalen, 1896, 291, 352.



In addition to the methods already referred to, pinol can be prepared by the action of alkali on α -terpineol chlorohydrin (see p. 263) and also by the action of zinc dust on *pinol glycol chlorohydrin* (XII), a substance which is formed when α -pinene (XI) is treated with hypochlorous acid.* By this method the



* Wagner and Slawinski, *Ber.* 1899, 32, 2070.

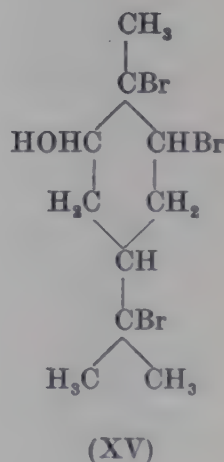
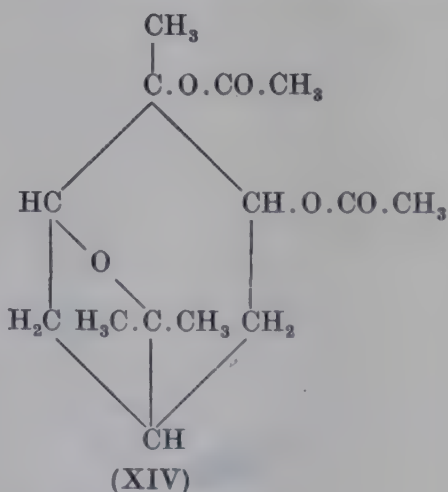
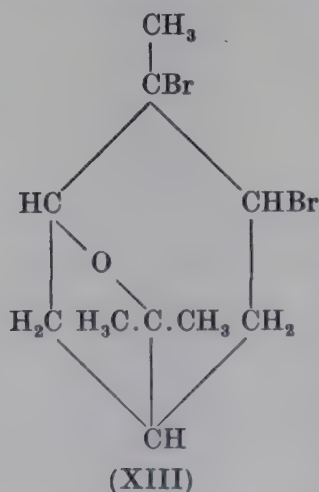
optically active pinols have been prepared, other methods yielding the externally compensated form.

According to Neave,* pinol is obtained also when sobrerol is distilled over finely divided copper at 300° .

Pinol is an oil, b.p. $183-184^{\circ}$, d_{20}^{20} 0.942, n_D^{20} 1.4714, possessing a marked camphoraceous odour. It can be most readily characterised by the preparation of the *dibromide*, m.p. 94° , or by the *nitrolamines* described below. Pinol is apparently readily racemised. The only evidence of the existence of the active form is that given by Wagner and Slawinski,† who state that the pinol prepared from the *d*-chlorohydrin yields on oxidation *d*-pinol glycol, although on bromination the *dl*-bromide is obtained.

Towards reducing agents it shows a very remarkable stability, but its unsaturation is apparent in its reactions with bromine. When pinol is treated with bromine in acetic acid solution *pinol dibromide* (XIII) is obtained. This bromide, which crystallises with great facility, is volatile in steam.‡ By the action of formic acid or on reduction with zinc dust and acetic acid, pinol dibromide yields *p*-cymene.§ With the latter reagent, in addition to the hydrocarbon, α -terpineol and *pinol glycol diacetate* (XIV), m.p. $97-98^{\circ}$, are also formed.

This diacetate results also from the action of either silver or sodium acetate on pinol dibromide. The *glycol* itself, m.p. 125° ,



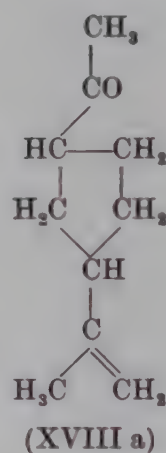
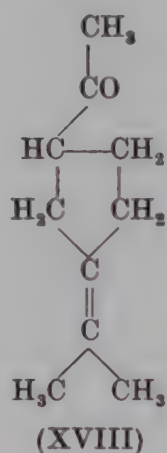
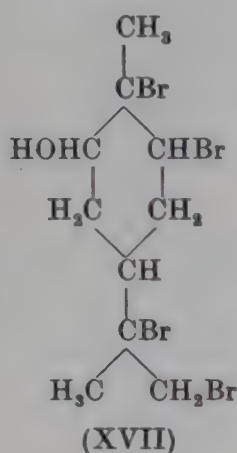
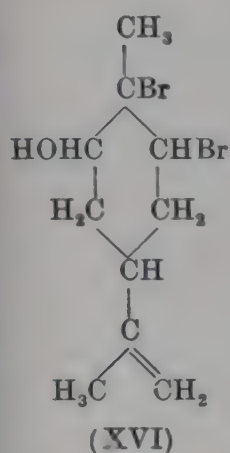
* *J.C.S.* 1912, 101, 514.

† *Ber.* 1899, 32, 2070.

‡ Wallach, *Annalen*, 1889, 253, 253.

§ *Ibid.* 1892, 268, 224.

can be prepared by treatment of the dibromide with silver oxide. By the action of alcoholic potassium hydroxide solution on the dibromide, pinol is regenerated, whilst oxidation with potassium permanganate yields terebic acid. When pinol dibromide is allowed to react with an excess of bromine, *pinol tribromide* (XV), m.p. 160° , is obtained.* This tribromide exhibits a number of interesting reactions. Treatment with silver acetate in ethyl acetate solution or quinoline in benzene solution leads to the formation of an isomeric dibromide, *isopinol dibromide* (XVI), m.p. 94° , from which a *tetrabromide* (XVII), m.p. 132° , can be prepared.†



Reduction of either pinol tribromide (XV) or *isopinol dibromide* (XVI) with zinc dust in acetic acid solution yields a ketone, *pinolone*, b.p. $214\text{--}217^{\circ}$, d^{20}_D 0.916, n^{20}_D 1.4660, which is probably not homogeneous, but a mixture of the two substances represented by formulae (XVIII) and (XVIII a). Wallach‡ has proved the constitution of pinolone and has suggested also the mechanism of the reactions involved in its formation.

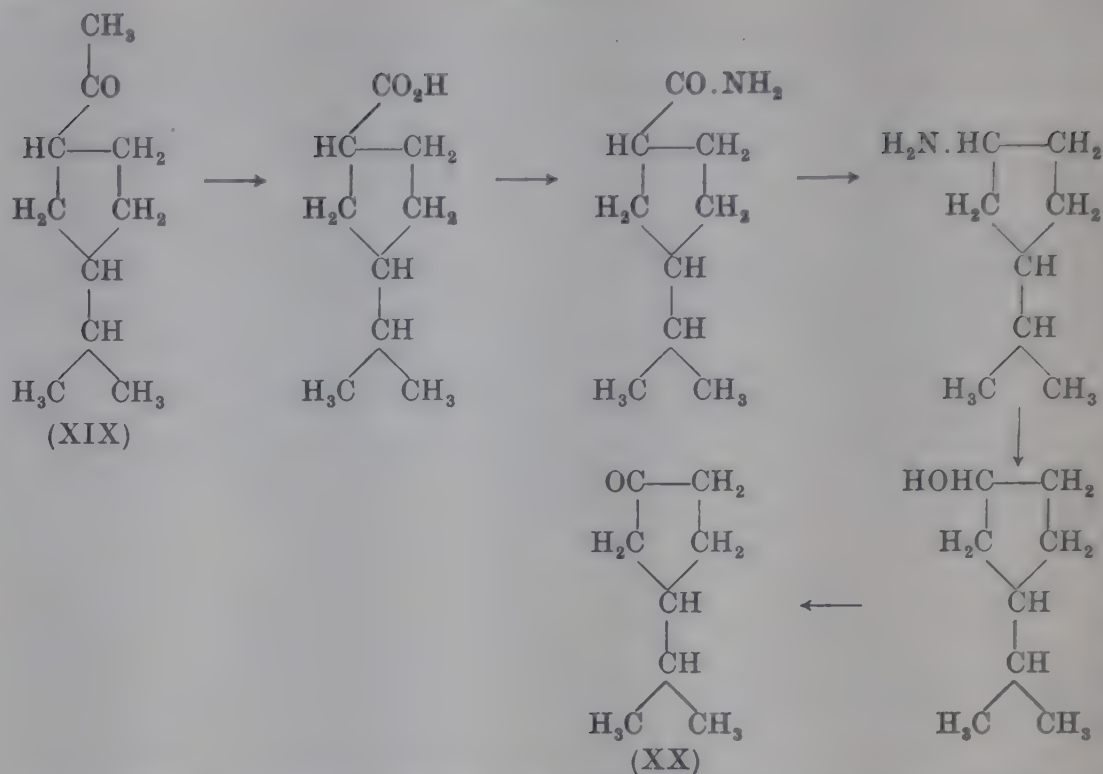
When pinolone is reduced catalytically it yields *dihydropinolone*,§ which, since it can be converted into *isopropylcyclopentan-3-one* (XX) by the reactions shown schematically on p. 442, must be 3-acetyl-isopropylcyclopentane (XIX).

* Wallach, *Annalen*, 1890, **259**, 324; 1894, **281**, 152.

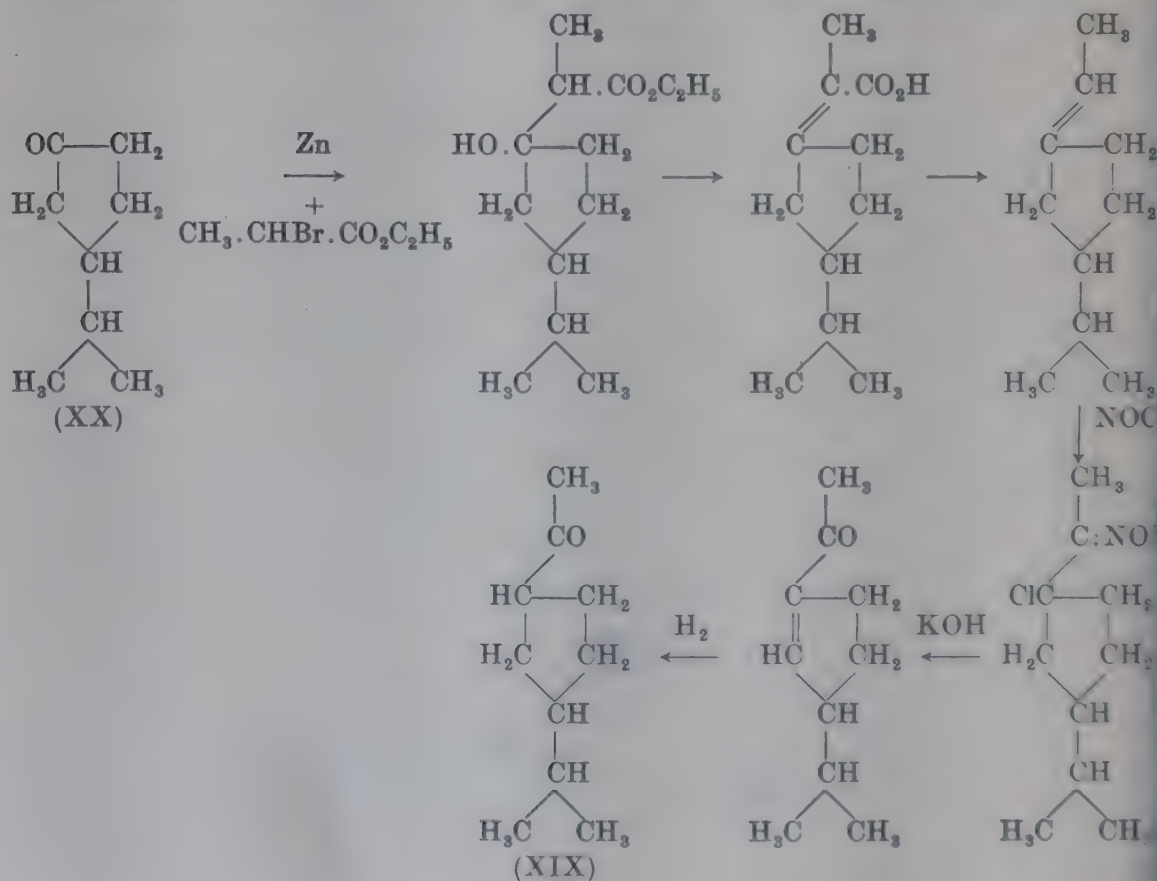
† *Ibid.* 1899, **306**, 269, 272.

‡ *Ibid.* 1911, **384**, 193.

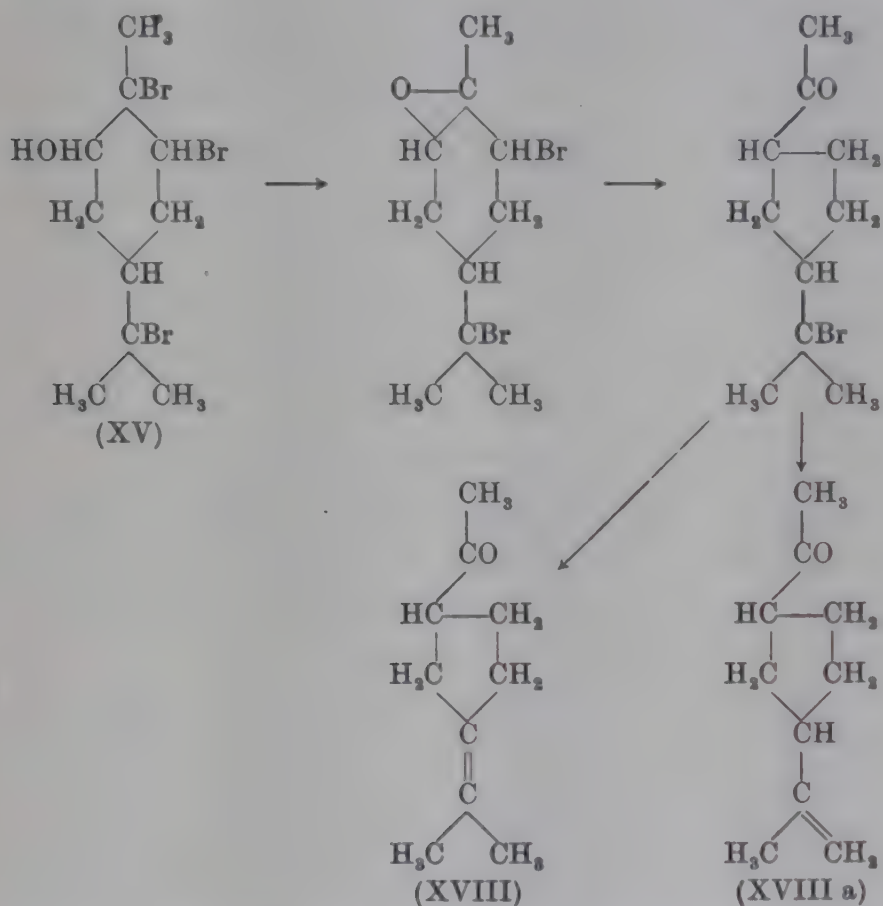
§ Dihydropinolone is also formed by the reduction of *isocamphor* (1-acetyl-3-isopropyl- Δ^1 -cyclopentene) (Wallach, *Annalen*, 1912, **392**, 69; Rimini, *Rend. della Soc. chim. Italy*, 1914, p. 27).



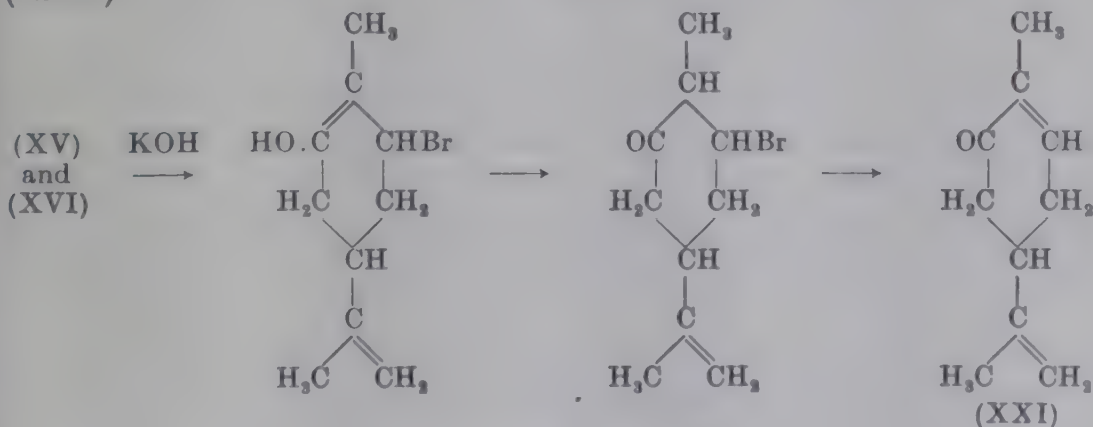
The evidence afforded by this degradation was fully confirmed by an elegant synthesis of *dihydropinolone* starting from *isopropylcyclopentan-3-one*. The steps involved are given below:



Whilst these ingenious experiments leave no doubt as to the constitution of the saturated ketone, they leave uncertain that of pinolone. It would appear to be probable that it is a mixture of the two substances (XVIII) and (XVIII a), and that it is formed from the bromides referred to above by the following series of reactions:

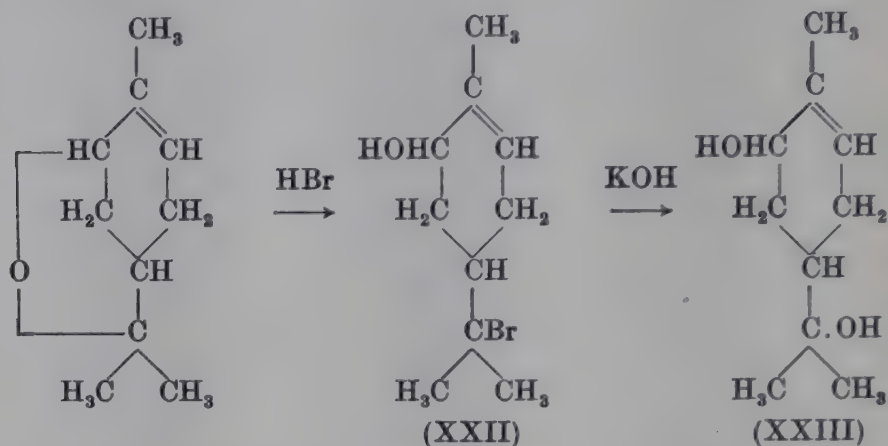


It is further of interest to note that both pinol tribromide and isopinol dibromide give on digestion with alkali *dl*-carvone (XXI).*

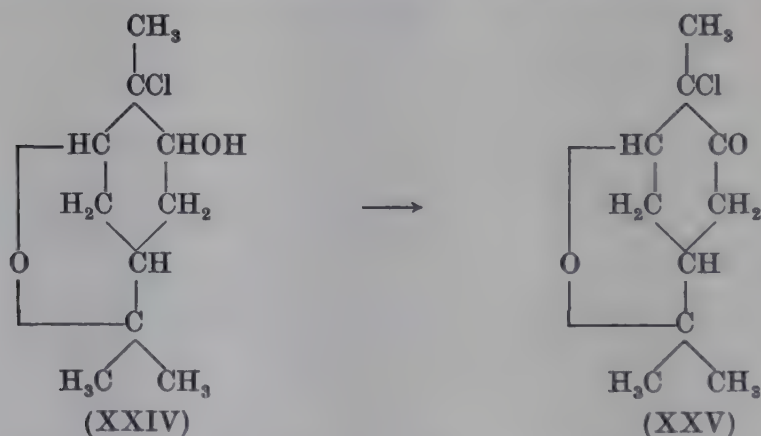


* Wallach, *Annalen*, 1911, 384, 193.

Although pinol contains an ethylenic linkage, it reacts abnormally with hydrogen bromide, the oxide ring undergoing fission with formation of a liquid *hydrobromide*, which must have formula (XXII) since, on treatment with alkali, it yields pinol hydrate (XXIII).*



With hypochlorous acid, however, the reaction proceeds normally with addition to the ethylenic linkage and formation of *cis-pinol glycol 1-chlorohydrin* (XXIV), m.p. $52-54^\circ$, and this, on oxidation with chromic acid, gives the *chloroketone* (XXV).†



Pinol gives very readily a *nitrosochloride*, m.p. $116-120^\circ$, which is bimolecular and on keeping passes into the monomolecular form, m.p. 131° .‡ From the nitrosochloride, Wallach prepared a number of *nitrolamines* which are very suitable for the characterisation of the oxide; mention may be made of the

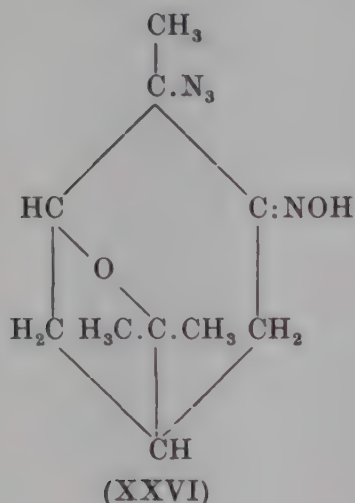
* Wallach, *Annalen*, 1890, 259, 313; 1896, 291, 351.

† Ginsberg, *J. Russ. Phys. Chem. Soc.* 1898, 30, 681.

‡ Wallach, *Annalen*, 1889, 253, 261; 1899, 306, 278.

nitrolpiperidide, m.p. 154°, and the *nitrolbenzylamide*, m.p. 135–136°.

Forster and van Gelderen* made the interesting observation that when pinol nitrosochloride was treated with sodium azide *pinol nitrosoazide* (XXVI), m.p. 160°, was formed. This azide is remarkably stable and is not attacked by dilute sulphuric acid or concentrated hydrochloric acid, so that unfortunately it was not possible to prepare the corresponding ketone.



The oxidation of pinol with potassium permanganate was very thoroughly investigated by Wagner† and Wagner and Slawinski.‡ They obtained in this manner *trans-pinol glycol*, m.p. 129°, which is isomeric with the *cis*-form, m.p. 123–124°, to which reference has been made already. Although the melting-points of the two glycols lie close together, they can be distinguished by the preparation of their *diacetates*, the *cis*-form melting at 97–98° and the *trans*- at 37–38°. According to Wagner and Slawinski, *d-pinol glycol* melts at 73–74.5°. As has been mentioned already the other products of the oxidation are terebic and terpenylic acids. When pinol is oxidised with nitric acid only terebic acid is obtained.

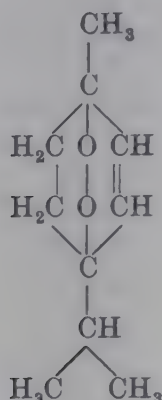
* *J.C.S.* 1911, 99, 2067.

† *Ber.* 1894, 27, 1644.

‡ *Ibid.* 1899, 32, 2067.

ASCARIDOLE

(Δ^2 -*p*-Menthene-1:4-dioxide or
1-Methyl-4-isopropyl- Δ^2 -cyclohexene-1:4-dioxide)



Ascaridole, $C_{10}H_{16}O_2$, one of the most remarkable of plant products, was first isolated from chenopodium oil (from *Chenopodium ambrosioides* var. *anthelminticum*) by Hüthig,* its constitution being subsequently established by the researches of Nelson and Wallach.

Hüthig found that ascaridole had the formula $C_{10}H_{16}O_2$ and that, when it was heated to $130-150^\circ$, it decomposed with explosive violence, the temperature rising to about 250° . On treatment with formic acid, *p*-cymene was obtained and this hydrocarbon, together with an unidentified ketone, resulted on reduction with zinc dust and acetic acid.

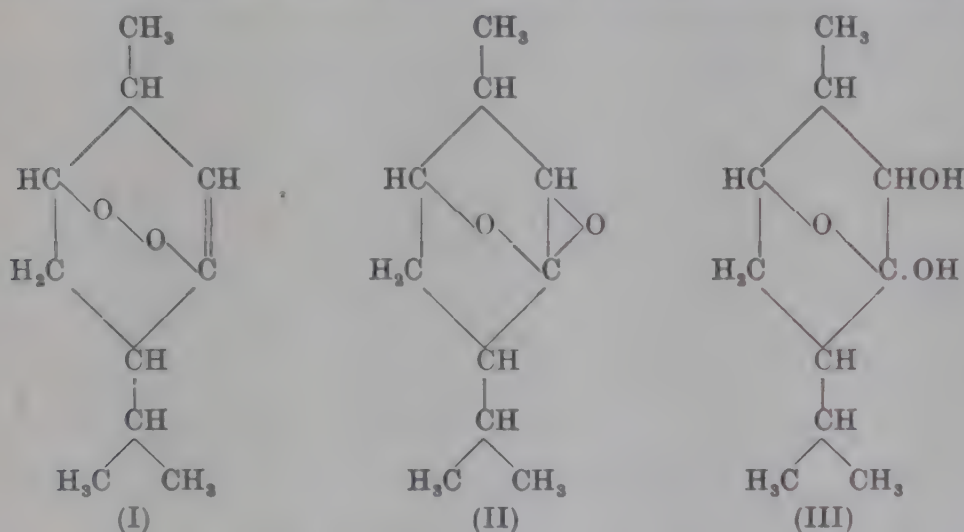
The first systematic study of this remarkable substance was made by Nelson.† He confirmed the observations of Hüthig regarding its tendency to decompose with explosive violence and he showed that it did not contain a hydroxyl or carbonyl group. On oxidation with ferrous sulphate, some isopropyl alcohol was formed but the main product of the reaction was not volatile in steam. This new substance was found to be a glycol, *ascaridole glycol*, $C_{10}H_{18}O_3$, m.p. $62.5-64^\circ$, b.p. $271-272^\circ$, $d_{20}^{20} 1.0981$, $n_D^{20} 1.4796$, $[\alpha]_D \pm 0^\circ$, and it was characterised by the preparation of a *monobenzoate*, m.p. $136-137^\circ$, and a *dibenzoate*, m.p. $116.5-117.5^\circ$.

* Schimmel's Report, 1908, April, p. 108.

† J. Amer. C.S. 1911, 33, 1404.

When ascaridole is decomposed by heating to 150° , a reaction best carried out in an inert solvent,* it yields an isomeric body, *ascaridole glycol anhydride*, b.p. $122-125^{\circ}/20$ mm., d^{15}_{20} 1.026, $[\alpha]_D -0.72^{\circ}$, from which, on hydration with dilute sulphuric acid, ascaridole glycol can be prepared. Nelson showed also that when the glycol was oxidised with potassium permanganate, two acids were formed; one of these, *ascaridic acid*, m.p. $116.5-117^{\circ}$, had the formula $C_{10}H_{16}O_5$, whilst the second, m.p. $186-187^{\circ}$, was, at the time, given the formula $C_{10}H_{16}O_6$.

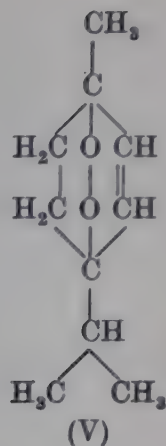
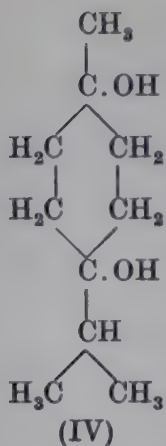
From these data Nelson suggested tentatively that ascaridole might be represented by (I) and the glycol by (III), formation of the latter taking place through the intermediate oxide (II).



Shortly afterwards Wallach† published an account of a study of the products formed from ascaridole on reduction with hydrogen using a palladium catalyst. He found that a crystalline solid (*A*) and an oil (*B*), volatile in steam, were formed. The solid (*A*) was found to be a new *terpinene-terpin* (1:4-terpin), m.p. $116-117^{\circ}$, which was optically inactive and was not identical with 1:8-terpin, which was approximately the same melting-point. It was evidently isomeric with the well-known terpinene-terpin, m.p. 137° (p. 304), since on treatment with hydrogen chloride it gave terpinene dihydrochloride, whilst on dehydration with oxalic acid 1:4-cineole (p. 433) was obtained. Since the terpinene-terpin must be represented by (IV), Wallach suggested that ascaridole was probably the dioxide (V).

* Henry and Paget, *J.C.S.* 1921, 119, 1722.

† *Annalen*, 1912, 392, 59.



The volatile oil (*B*) was found to be a mixture of *alcohols*, b.p. 207–209°, giving on dehydration a *menthone*, b.p. 173·5–175·5°, which was not identified.

In the light of Wallach's results, the formulae suggested by Nelson for ascaridole glycol anhydride and ascaridole glycol required modification, and this author in 1913* published an account of his further investigations. He now showed that when the anhydride was hydrated with sulphuric acid, in addition to ascaridole glycol, m.p. 62·5–64°, a second glycol, *ascaridole-β-glycol*, m.p. 103–105°, was formed, together with an *erythritol*, *p-menthane-1:2:3:4-tetrol*, m.p. 128–130°. The *β-glycol* was readily converted into thymol on treatment with sulphuric acid, whilst, on dehydration, the erythritol gave a ketone, the constitution of which was not determined.

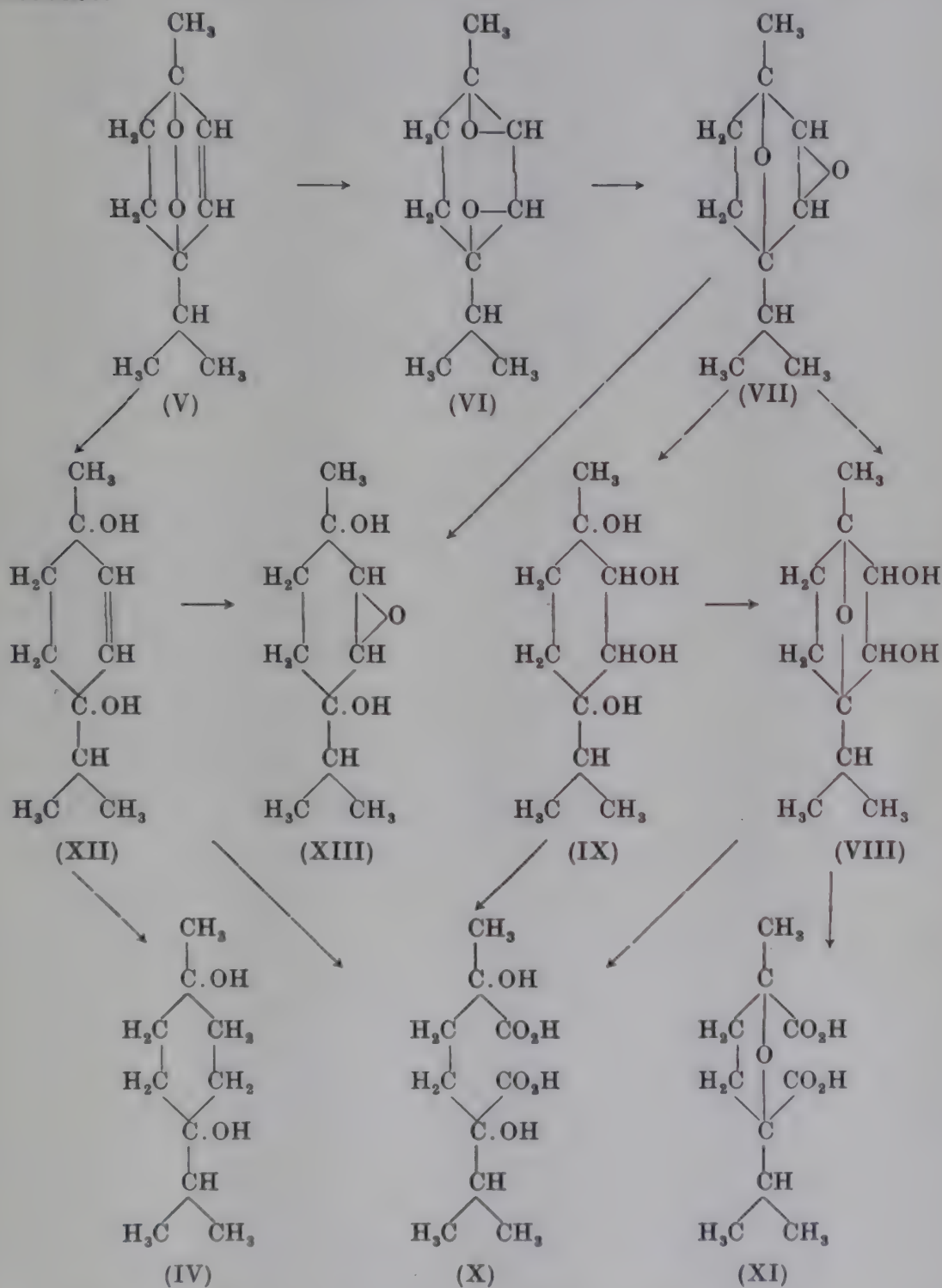
Accepting Wallach's formula (V) for ascaridole, Nelson considered the anhydride to be best represented by (VI) and the glycol by (VIII), a substance (VII) being intermediate in its formation; whilst the erythritol (IX) was a direct hydration product. It is, however, probable that the anhydride itself has formula (VII), the formation of which by the isomerisation of ascaridole is easy to understand.†

Confirmation of the structures assigned to the erythritol and the glycol was furnished by a renewed study of the products obtained on oxidation with potassium permanganate. From the erythritol, *α-methyl-α'-isopropyl-α'-dihydroxyadipic acid* (X) was obtained, and the higher melting acid previously given the formula $\text{C}_{10}\text{H}_{16}\text{O}_6$ (see above) was found to be identical with this.

* *J. Amer. C.S.* 1913, 35, 84.

† Thoms and Dobke, *Arch. Pharm.* 1930, 268, 128.

The acid, m.p. 116.5–117°,* ascaridic acid, is probably 1:4-cineolic acid (XI), since it yields an *anhydride*. A detailed study of the properties of this acid should furnish results of considerable interest.

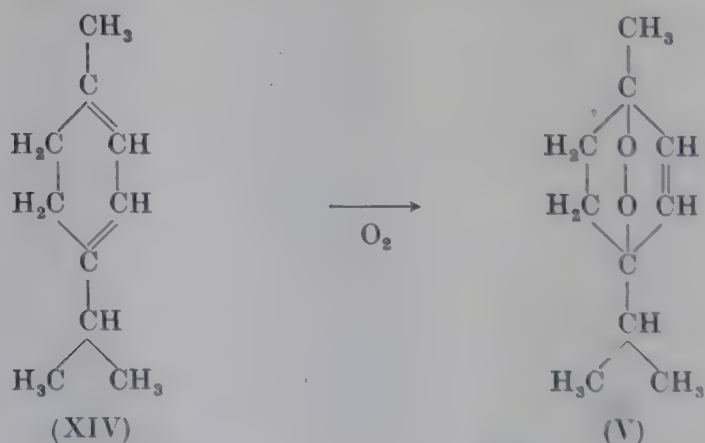


* Henry and Paget (*J.C.S.* 1921, 119, 1722) give the melting-point as 121°, which has been confirmed by Elson, Gibson and Simonsen (compare p. 185).

The structure (V) for ascaridole is supported also by the results of further studies on its hydrogenation. Richter and Presting* and also Bodendorf† have shown that by the use of a limited amount of hydrogen, with a palladium catalyst, it is possible to obtain Δ^2 -*p*-menthene-1:4-diol (XII), the structure of which is proved by oxidation to the acid (X); complete reduction gives *cis*-1:4-terpin (IV), m.p. 117°, as already found by Wallach (p. 447). The menthenediol may also be obtained by the disproportionation of ascaridole with palladium, a reaction which, according to Richter and Presting, proceeds with considerable vigour. These authors, by treatment of the menthenediol with perbenzoic acid, obtained 2:3-oxido-*p*-menthane-1:4-diol (XIII), m.p. 102°, which they suggested to be identical with the β -glycol isolated by Nelson, though unfortunately a direct comparison could not be made.

It should also be mentioned that Henderson and Robertson‡ obtained by the oxidation of sabinene with hydrogen peroxide a *glycol*, m.p. 172°, to which the structure (VIII) was assigned. This material is presumably a stereoisomer of the α -glycol.

A synthesis of ascaridole has been described by Schenck and Ziegler§ who have shown that α -terpinene (XIV) undergoes 1:4-addition of oxygen when irradiated in dilute solution in the presence of a fluorescent dye, such as chlorophyll. The ascaridole obtained in this way had m.p. 2.5°. The reaction is of great interest, and suggests that the formation of ascaridole in nature may well occur by a similar process.



* Ber. 1931, 64, 878.

‡ J.C.S. 1923, 123, 1849.

† Arch. Pharm. 1933, 271, 1.

§ Naturwiss. 1944, 32, 157.

Ascaridole is a somewhat viscid oil, b.p. 96–97°/8 mm., $d_{20}^{20} 0.9985$, $n_D^{20} 1.4769$, $[\alpha]_D + 0.7^\circ$. The conversion of the dioxide into the isomeride, ascaridole glycol anhydride, is most conveniently carried out by dissolving the oxide in xylene and heating the mixture to 130–150°.* On completion of the very vigorous reaction, the volatile solvent is removed by steam and the anhydride can then be purified by distillation. Ascaridole is decomposed with explosive violence by sulphuric, hydrochloric, nitric and phosphoric acids, and does not yield any crystalline derivatives. It is used in medicine in the treatment of hookworm disease.

* Henry and Paget, *J.C.S.* 1921, 119, 1722.

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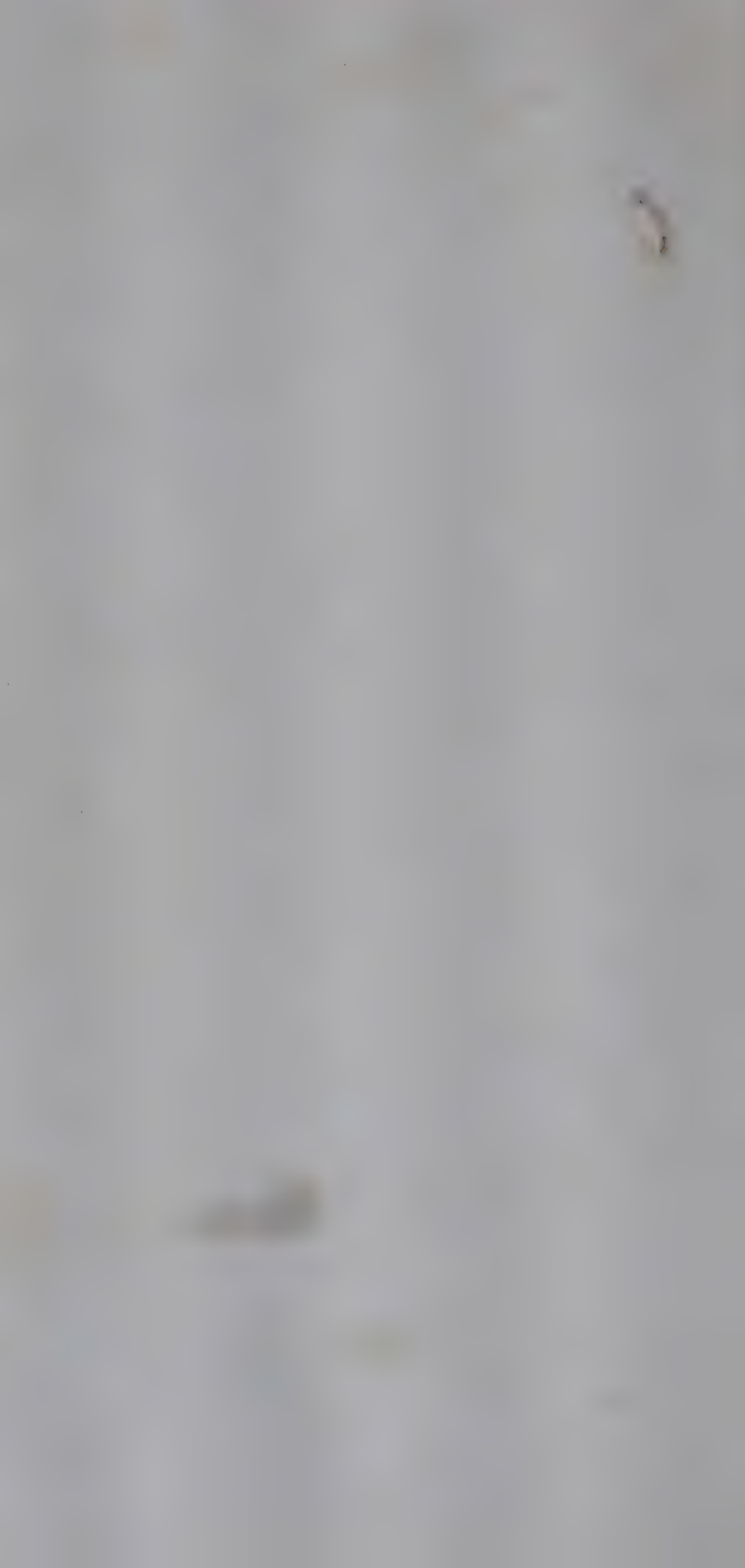
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